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Abstracts of Communications

STOCKHOLM 1957

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Abstracts of Communications

STOCKHOLM 1957

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INDEX OF AUTHORS

Albanus, L. 5
Allgoth, A.-M. 5
Andersen, H. T. 6
Andersen, P. 7
Andersin, E. 9
Andersson, B. 10
Andersson, S. 11, 12, 13
Andersson-Cedergren, E. 15
André, T. 16
Asmussen, E. 17

Bárány, F. R. 18
Bergen, U. 9
Berglund, E. 19
Bergström, L. 20
Bergström, R. M. 20, 21
Bertler, Å. 22
Bojesen, E. 23
Borst, H. 19
Buchthal, F. 24, 25
Bugge-Asperheim, B. 27

Campbell, D. 27
Carlsen, F. 28
Carlsson, A. 22
Carlsten, A. 29
Clemedson, C.-J. 29, 30, 31

Diamant, B. 32
Diamant, H. 33
Döbeln, W. von 34
Duff, F. 19
Dyrberg, V. 35

Edgren, B. 35
Edman, K. A. P. 36
Egense, J. 23, 37
Elwin, C. E. 12, 13
Engbæk, L. 24
Enger, P. S. 38
Eriksen, L. 39
Erikson, G. 39
Erikson, H. 39, 40
Euler, C. von 40, 41
Euler, U. S. von 42

Fernö, O. 43, 44
Finnilä, M. J. 9
Frankenhaeuser, B. 45
Fredriksson, T. 29, 47
Fries, B. 5, 47

Gemzell, C. A. 48
Giacobini, E. 49
Graf, K. 5, 50
Graf, W. 5, 51
Grant, R. 51
Gräsbeck, R. 52
Green, J. D. 40
Gribbe, P.-O. 54
Grimby, G. 29
Guld, C. 54

Haaranen, A. 56
Hagbarth, K. E. 57, 58
Håkansson, C. H. 59
Halme, A. A. 60, 62
Hammel, H. T. 63
Hanngren, Å. 64
Hansson, C-H. 65
Hansson, E. 65
Harboe, M. 66
Hartelius, H. 30
Hartiala, K. J. W. 60, 62, 67
Hauberg Johansen, S. 68
Hintsanen, M. 56
Hirsjärvi, E. 69
Hirvonen, L. 54, 70
Hisdal, B. 71
Högberg, B. 32, 43, 44, 72
Holmberg, G. 30
Holmstedt, B. 33, 72, 73
Hougs, W. 35, 68, 74
Hultman, H. 31

Iisalo, E. 75
Ingelman-Sundberg, A. 75, 76

Jahn, U. 25
Jalavisto, E. 56, 77
Jäntti, K. 78

Kaada, B. 79, 80
Kågström, E. 82
Kallio, I. V. I. 83
Kalliola, H. 70

Karlog, O. 84
Karvonen, M. J. 84
Kassila, O. J. 60
Kauhanen, E. 56
Kenedi, T. 85
Knappeis, G. G. 28
Kobinger, W. 86
Koefoed-Johnsen, V. 87
Krayer, O. 88
Krog, J. 89
Kugelberg, E. 57, 58

Lagergren, B. 90
Lagerlöf, H. 85, 90
Lähdevirta, J. 91
Landgren, S. 92
Lang, H. 70
Lange Andersen, K. 27, 63
Larsson, S. 93
Leivestad, H. 6
Lennox, M. A. 94
Liljedahl, S. O. 96
Liljestrand, A. 96
Lind, J. 54
Lindblom, U. F. 97
Linderholm, H. 98
Lindgren, L. 75, 76
Lindgren, P. 51, 99
Lishajko, F. 42
Lorentzen, F. V. 66
Løyning, Y. 63
Lund, A. 100, 101
Lundin, S. J. 102
Lundquist, F. 102
Lybeck, H. 103, 105

Mattsson, O. 96
Monroe, R. 19

Næss, K. 106
Nederström, A. 56
Nielsen, M. 17
Niemi, M. 106
Nilsson, J. 22
Nisell, O. 107
Nyberg, W. 52

Olsson, S. 108
Oscarsson, O. 109
Östling, G. 111

Paasonen, M. K. 88
Pascoe, J. E. 112
Pekanmäki, K. A. 62
Pekkarinen, A. 113
Peltonen, T. 70
Perman, G. 52, 85, 90
Pernow, B. 96
Persson, A. 45
Persson, N. 10
Piha, R. S. 9, 91
Pulkkinen, M. 115

Räihä, N. 84, 116
Raina, A. 91
Refsum, H. E. 71
Reizenstein, P. 52
Robbe, H. 48
Rosell, S. 5, 50
Rosén, A. 51
Rosenfalck, A. 117
Rosenfalck, P., 117, 118
Rosengren, E. 22
Rud, J. 120
Rudewald, M. B. 85
Rushton, W. A. H. 121
Rydén, G. 75, 76

Salovaara, A. 70
Sandberg, F. 75, 76
Savola, P. 122
Schambye, P. 124
Scholander, P. F. 6, 63, 89, 125
Schou, J. 126
Schreiner, G. 19
Sjöqvist, F. 72
Sjöstrand, F. 15
Sjöstrand, T. 126
Skou, J. C. 127
Söderberg, U. 41, 128
Sörbo, B. 29
Sperber, I. 129
Steen, J. 38
Steg, G. 131
Sten-Knudsen, O. 132
Stovner, J. 133
Ström, G. 48
Sundnes, G. 125

Tala, E. O. J. 83
Tarding, F. 124
Tham, R. 73
Thesleff, S. 134
Thon, I.-L. 32
Thorshauge, C. 74
Tribukait, B. 135

Ursin, H. 79, 80
Uvnäs, B. 13, 32, 44, 51, 72

Valen, E. 136
Whittaker, V. P. 136
Wollheim, F. 138
Wolthers, H. 102
Wretlind, A. 139

Albanus, L. and B. Fries (Department of Pharmacology, Veterinärhögskolan, Stockholm, Sweden): PERMEABILITY OF THE PERITONEUM IN VITRO.

In connection with an experimental study of the absorption from and exsudation to the peritoneal cavity, a study was made of the permeability of the peritoneum in vitro. An apparatus for perfusion of thin tissue-membranes designed by DAY (1952) and modified by STEINCKE (1953) was used. Peritoneal membranes from rabbits were used throughout. The membranes were perfused with normal saline solution as well as saline added with the enzyme hyaluronidase and an inhibitor of hyaluronidase, polyphloretin phosphate, in order to study the eventual influence of these drugs on the permeability of the peritoneum. The results of this investigation are discussed.

Day, T. D., J. Physiol. 1952. *117*. 1.
Steincke, K., Acta Pharm. et Toxicol. 1953. *9*. 27.

Allgoth, A.-M., K. Graf, W. Graf and S. Rosell (S:t Eriks Hospital, IInd Medical Service, and Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): STUDIES ON HUMAN LIVER BLOOD FLOW BY MEANS OF RECORDING THE THERMAL CONDUCTIVITY OF THE PARENCHYMA.

The blood flow of the human liver has been recorded continuously with the aid of heated thermocouples ad modum HENSEL.

Observations have been made on subjects in a basal state and after administration of certain drugs. Particular attention

has been paid to the effect of adenosine triphosphoric acid, epinephrine, norepinephrine, histamine and pitressin. The findings are discussed in relation to previous reports on corresponding topics.

Andersen, H. T. (Institute of Zoophysiology, University of Oslo, Norway): DIVING METABOLISM IN THE DUCK.

It is known from previous investigations that when a duck is submerged it exhibits a series of diving reflexes: bradycardia, reduced muscular circulation, and small oxygen debt after a dive.

In the present investigation the oxygen consumption has been found to decrease exponentially with time. The body temperature also dropped steadily although only the head was submerged. This indicates that the total metabolic rate is lowered during diving.

Oxygen and carbon dioxide tensions developed during the dive are described in terms of the oxygen-carbon dioxide diagram. The effect of repeated dives on these tensions will be discussed.

Andersen, H. T., H. Leivestad and P. F. Scholander (Institute of Zoophysiology, University of Oslo, Norway): »AIR DIVING» IN FISHES.

When diving mammals and birds submerge they exhibit a series of characteristic phenomena. The heart rate, in spite of exercise, slows down. Lactic acid accumulates in the muscles but only very little leaks out into the circulation because of a strongly depressed blood flow through the muscles. In the recovery after a dive lactic acid from the muscles floods the blood and circulation is greatly increased. These and other adjustments are strikingly developed in many diving mammals and birds and have been found, more or less pronounced, in all warmblooded animals where they have been looked for. Also man may have a pronounced bradycardia during diving

in spite of vigorous swimming. Preliminary unpublished experiments performed years ago indicated that similar mechanisms operate in the dogfish when taken out of water. In the present investigation cod have been subjected to a condition of asphyxia by taking them out of the water for 4 minutes and then placing them back again. The level of lactic acid in the arterial blood remained low (5—10 mg %) during the air exposure but rose 5—10-fold in the recovery and then gradually resumed the low basal value. In contrast the lactic acid of the back muscles rose steeply during the air exposure and was gradually eliminated when the fish was placed in water again. The heart rate slowed down to half of the normal value during air exposure. Violent muscular activity during air exposure did not break bradycardia. The above data demonstrate a metabolic isolation of the muscles during air exposure, probably caused by a reduced circulation through the muscles. This mechanism, accordingly, is very much like that which operates in mammals and birds during diving.

Andersen, P. (Anatomical Institute, University of Oslo, Norway): ELECTROPHYSIOLOGICAL STUDIES OF THE VENTRAL HIPPOCAMPAL COMMISSURE IN RABBIT AND CAT.

Impulses conveyed by the ventral hippocampal commissure (*psalterium ventrale*) were studied by the evoked potential technique. The form of the potentials obtained in rabbits and cats was similar.

1. The fimbrial potential evoked by contralateral fimbrial stimulation consisted of a diphasic positive/negative potential of 2—3 msec duration followed by a negative wave lasting for 4—12 msec. Both components were greatest when stimulating and recording near the hippocampal border and they had the same threshold.

The diphasic potential was absolute refractory for 1.3 msec and relative refractory for 4 msec. It followed stimulus frequencies of 250/sec without change in amplitude. Local

application of strychnine at the site of recording had no effect, whereas novocaine abolished the response. The potential resisted complete asphyxia for a period of 15—33 minutes.

The negative wave was absolute refractory for 5 msec and relative refractory for 20 msec. Repetitive stimulation of 3—40/sec caused recruitment. The negative wave followed stimulus frequencies up to 120/sec. Strychnine enhanced and novocaine abolished the amplitude of the negative wave simultaneously with the diphasic potential. The negative wave decreased after 1.5—2 minute asphyxia and was abolished after 3—4 minutes. Occasionally a small negative wave remained for 5—8 minutes during asphyxia.

Both components were abolished by sectioning the ventral hippocampal commissure. The diphasic potential is interpreted as due to impulses travelling in the commissure; the negative wave as due to postsynaptic and antidromic activity of hippocampal neurones. Impulses were conducted at 2.5—4 m/sec in the cat and at 6—7 m/sec in the rabbit. Fiber measurements in cats gave diameters of 0.5—1.0 μ, none above 2.0 μ.

2. Stimulation of the hippocampus evoked in the contralateral symmetrical area a potential consisting of a diphasic positive/negative deflection with a negative spike superimposed on the positivity. The duration of the positive component was 15—25 msec and of the negative wave 60—100 msec. The total amplitude measured 0.2—6 mV. The stimulus threshold was about one fifth of that of the corpus callosum potential. Repetitive stimulation at 5—35/sec caused recruitment of the diphasic potential and increase of the spike with shortening of its latency. Depth stimulation with micro-electrodes was most effective in the pyramidal layer of CA_1 and CA_4. Depth recording revealed polarity change in the *stratum radiatum* and another responsive area in *hilus fasciae dentatae*. The spike showed a maximum in the pyramidal cell layer. Strychnine enhanced the potential, mainly the spike and the negative component; novocaine had only a small effect. Asphyxia abolished the spike after 1—2.5 minutes followed by elimination of the negative component while the positive wave remained for 3—5 minutes. Stimulation of the entorhinal area elicited

direct impulses to the contralateral hippocampus through the ventral hippocampal commissure.

The positive component of the hippocampal commissural potential is interpreted as depolarization in the layer of the apical dendritical shafts (synaptic potential), the spike as firing of the pyramidal cells, and the negative component partly as spread of the depolarizing current over the rest of the neurone (dendritic potential), partly as postsynaptic firing of hippocampal neurones.

Andersin, E., U. Bergen, M. J. Finnilä and R. S. Piha (Institute of Physiology, University of Helsinki, Finland): THE EFFECT OF 5-HYDROXYTRYPTAMINE ON THE OXYGEN CONSUMPTION IN RATS.

In a previous paper it was reported that histamine in wax mineral oil depot when administered subcutaneously decreases the oxygen consumption in rats and that the action lasts for about a week (APAJALAHTI and PIHA 1954). Since 5-hydroxytryptamine (serotonin, enteramine) has certain physiological activities which resemble those of histamine, a study on the effect of this drug on oxygen consumption seemed profitable.

Twelve female rats weighing between 155 and 190 g were used for these experiments. The animals kept on carbohydrate diet were divided into three groups (I, II and III) each comprising four rats. 5-Hydroxytryptamine creatinine sulphate in bee's wax mineral oil mixture at 39° C was administered in a single subcutaneous injection. The oxygen consumption of the groups (4 rats together) was measured according to the method described in detail earlier (APAJALAHTI and PIHA 1954).

The experiments were carried out as follows. The basal oxygen consumption was determined 6 to 7 times. The rats of the groups I, II and III then received a depot of 100, 200 and 300 mg of 5-hydroxytryptamine/kg bodyweight, respectively. Thereafter the oxygen consumption was recorded at intervals over a period of about 30 days.

In group I a distinct fall in oxygen consumption was observed on the second day after the injection. The oxygen consumption decreased from the mean basal value of 14 ml/min to the minimum of about 11 ml/min remaining at the low level for about two weeks, after which the oxygen consumption increased again. The most typical effect was observed on the days when the rats had been starved for 12 hours before the measurement.

For the rats of groups II and III food was supplied continuously during the experimental period. In both of the groups a lowered rate of the oxygen consumption was observed which did not occur noticeably until the fourth day after the drug administration. The mean initial value of 15.6 ml/min fell to the minimum of 11 ml/min found on the fifth day. After three weeks from the injection the oxygen consumption was restored to the normal level again.

The 5-hydroxytryptamine depot was found to be resorbed during the course of the experiments. Therefore it is probable that the organism was continuously under the action of this drug. It is concluded that it may be 5-hydroxytryptamine that has a lowering effect on the oxygen consumption. The influence of the dose and that of the temperature on the results are discussed.

Apajalahti, A. N. I. and S. Piha, Acta Physiol. Scand. 1954. *31*. 97.

Andersson, B. and N. Persson (Department of Physiology, Veterinärhögskolan, Stockholm, Sweden): PRONOUNCED HYPOTHERMIA ELICITED BY PROLONGED STIMULATION OF THE »HEAT LOSS CENTRE» IN CONSCIOUS GOATS.

It has earlier been shown (ANDERSSON, GRANT and LARSSON 1956) that electrical stimulation of a restricted area ventral to the anterior commissure causes polypneic panting, peripheral vasodilatation and inhibition of physiologically induced shivering in the conscious goat. This area is part of the

region of the brain stem where local heating mobilizes heat loss mechanisms in the cat (MAGOUN, HARRISON, BROBECK and RANSON 1938).

Experiments were performed in which this »heat loss centre» was continuously stimulated for up to three hours with the goats placed in an environmental temperature of minus 6 to minus 7° C. During the first two hours of electrical stimulation the rectal temperature fell evenly 4 to 5° C per hour. Having reached a level of 29.5° C after a little more than two hours of stimulation it remained fairly constant to the end of stimulation. Peripheral vasodilatation and polypnea persisted during the first two hours of stimulation although the respiratory frequency started to decline after 15 minutes of stimulation. Shivering was inhibited as long as the stimulation lasted. When the rectal temperature had fallen to 29.5° C there were difficulties of standing, muscular stiffness, drowsiness and markedly decreased blood flow in accessible veins. The blood glucose had then reached renal threshold level. A most violent shivering started immediately after the end of stimulation. After three hours' exposure to an environmental temperature of minus 7° C the rectal temperatures of normal goats were found to be slightly above normal and no increase in blood sugar level was seen.

Andersson, B., R. Grant and S. Larsson, Acta Physiol. Scand. 1956. 37. 261.

Magoun, H. W., F. Harrison, J. R. Brobeck and S. W. Ranson, J. Neurophysiol. 1938. 1. 101.

Andersson, S. (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): THE INHIBITORY EFFECT OF HCl INSTILLATION INTO ANTRUM OR DUODENUM ON THE GASTRIC ACID SECRETION IN PAVLOV POUCH DOGS.

The role of hydrochloric acid in regulating the HCl secretion in the stomach was first suggested by SOKOLOV (1904). Since then many authors have shown that the presence of acid

in the antral-duodenal portion of the gastrointestinal tract inhibits the gastric acid secretion both in man and dogs.

The purpose of the present experiments has been to determine if this inhibitory mechanism is situated in the antrum or the duodenum or in both of them. In case of the last mentioned possibility it is of interest to know the quantitative relations of these two parts in determining the secretory function of the stomach.

On Pavlov pouch dogs the antrum was separated from the rest of the stomach by a mucosal diaphragm at the antrum-corpus border. The gastrointestinal passage was reestablished by gastrojejunostomy. The pylorus was then divided and the duodenum closed. Antrum was provided with a simple cutaneous fistula and a second entrance through an anastomosed ileal loop leading to a second cutaneous fistula. Another ileal loop permitted access to the upper part of the duodenum through a third cutaneous fistula. After these procedures the animals showed a very high spontaneous fasting secretion.

This spontaneous secretion could be almost completely inhibited by instillation of N/10 HCl into the duodenum. A considerably smaller inhibition was obtained when the acid was instilled into the antrum. However, a total inhibition could be obtained only if the acid was instilled into both antrum and duodenum simultaneously.

Andersson, S. and C. E. Elwin (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): THE EMETIC ACTION OF ESTERS OF SOME AMINO-ACIDS.

In the course of an investigation of the ability of amino-acid-esters to reduce gastric acidity, it was observed that certain of these compounds had a profound emetic effect. We have therefore made a detailed study of the emetic effect of three of these esters, *viz.* isopropylester of phenylalanin, isobutylester of valine and isopropylester of glutamic acid.

The investigation was performed on dogs with gastric and

duodenal fistulas. Emesis was observed when the esters were given orally even in doses as small as 0.5 ml. In every case there was a 5 to 10 minute latency period before emesis, independent of the route of administration of the esters, *i.e.*, whether given by mouth, into the stomach or the duodenum. It was preceded by nausea (restlessness, lickings, yawns) for 1—2 minutes. The esters were given as a suspension in 10 ml isotonic NaCl. No difference between the three esters was observed. Neither NaCl nor alcohol, nor amino-acid, nor the ester-hydrochloride was found to have any emetic effects.

It has been possible to show that the emetic response could be evoked from the upper parts of the duodenum but probably not from the stomach and not from the duodenum beyond 50—60 cm. Introduction of the esters into the isolated antrum of a dog did not produce emesis. However, when the esters were placed in the duodenum there was a uniform and consistent response. In an antrum-resected dog emesis was produced following administration of the esters into the duodenum. In several dogs where rubber-balloons were placed into the duodenum just distal to the pylorus no emesis was caused by oral administration of the esters, but emesis was produced by the introduction of the esters into the duodenum distal to the balloon.

The emetic action could be blocked by lidocaine or atropine given locally in the stomach or duodenum but not by atropine given subcutaneously. After each emesis caused by the amino-acid-esters a refractory period of 1—2 hours followed when emesis could not be produced as easily as before.

Andersson, S., C. E. Elwin and B. Uvnäs (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): THE EFFECT OF ANTRAL RESECTION ON THE GASTRIC ACID SECRETION IN PAVLOV POUCH DOGS WITH EXCLUDED ANTRUM AND DUODENUM.

Exclusion of the antrum and duodenum from the normal gastrointestinal passage causes great changes in the acid secre-

tion from a Pavlov pouch. The 24-hour secretion is augmented, the secretory responses to insulin hypoglycemia and to histamine is elevated and a tendency to spontaneous fasting secretion appears.

The observations, considered as a whole, suggest an increased secretory response of the Pavlov pouch to various secretory stimuli. This heightened secretion might be due either to removal of inhibitory influences, resulting in increased excitability of the parietal cells, or to an increase of stimulating factors.

Gastrin is released from the antral mucosa in response to chemical and mechanical stimuli. In the last few years the conception, that a lower antral pH tends to inhibit the liberation of gastrin has been more and more generally accepted. A role of gastrin in the nervous phase of secretion has been suggested by UVNÄS (1942) and others. Recently, GREGORY (1957) has performed very convincing experiments, in which he caused HCl secretion in a Heidenhain pouch by sham feeding only when the gastric juice of the stomach was prevented from coming in contact with the antral mucosa.

Our own experiments agree with these observations. The extent to which antrum hyperfunction was responsible for the increased secretion from the Pavlov pouch in »antral-duodenal excluded» dogs was studied in a series of experiments on these dogs after antral resection.

The following results were obtained after antrum resection: the increased 24-hour secretion was reduced to about the original level. The heightened secretory response to insulin hypoglycemia returned to the same level as before antrum-duodenum exclusion. The increased secretory response to histamine remained elevated. The spontaneous secretion fell but did not reach the low preoperative secretory rate.

These results will be discussed.

Uvnäs, B., Acta Physiol. Scand. 1942. 4. Suppl. XIII.
Gregory, R. A., personal communication 1957.

Andersson-Cedergren, E. and F. S. Sjöstrand (Laboratory for Biological Ultrastructure Research, Department of Anatomy, Karolinska Institutet, Stockholm, Sweden): THE ULTRASTRUCTURAL ORGANIZATION OF THE CONTRACTILE ELEMENTS IN SKELETAL MUSCLE.

By means of high resolution electron microscopy the form, dimensions, and arrangement of the contractile units of frog skeletal muscle, the myofilaments, have been studied at various degrees of shortening and stretch of the sarcomeres. With shortening the mean diameter of the myofilaments in the A-band increases in proportion to the shortening. From about rest length to the states of maximum shortening analyzed in this study, the A-band as well as the I-band width decrease. The contours of the myofilaments become increasingly irregularly spiny with shortening. Numerous cross bridges connect adjacent myofilaments. In the dense zone of the A-band, the myofilaments are split into a number of branches, the mean diameters of which may fall into two size classes. The A-band myofilaments are continuous with the I-band filaments. Stretching the sarcomeres above rest length is accompanied with a slight decrease of the mean diameter of the A-band myofilaments and a disappearance of the split zone of the A-band. The A-band width is not changed or only little affected by stretch, the lengthening being due primarily to an increase of the I-band width.

Subunits with a diameter of 20 Å or less have been observed in the myofilaments presumably arranged in a helical fashion. Shortening from rest length, that is in the physiological range, may be interpreted as associated with a folding up or a change in the helical arrangement of the subunits of the myofilaments. This change is assumed to represent an intermolecular or supramolecular change of the structural organization with intact α-configuration of the peptide chains. The cross striations of the sarcomere depend primarily on different states of the myofilaments. The I-band part represents the zone of the myofilaments where its subunits are most stretched. During

shortening, the I-band part of the myofilaments are transferred to the A-band condition.

These results are in obvious contradiction to those of HANSON and HUXLEY (1955) and HUXLEY and NIEDERGERKE (1954). The explanation might partially be that their studies mainly concentrated on muscle fibers and fibrils which had been stretched over rest length.

Hanson, Jean and H. E. Huxley, Symposia Soc. Exper. Biol. 1955. *9*. 228.

Huxley, A. F. and R. Niedergerke, Nature, London, 1954. *173*. 971.

*André, T. (Department of Pharmacology, Veterinärhögskolan, Stockholm, Sweden): STUDIES ON THE DISTRIBUTION OF TRITIUMLABELLED DIHYDROSTREPTOMYCIN AND TETRACYCLINE IN THE BODY.

The synthesis of radioactive dihydrostreptomycin and tetracycline is described. Exchange reactions, the use of various isotopes and their advantages and drawbacks are discussed. Analyses and radioactivity determinations are outlined. The autoradiographic technique was adapted to the requirements imposed by the water-solubility of dihydrostreptomycin and tetracycline and also to the desire to obtain full-section autoradiograms, *e.g.*, of whole mice.

The disappearance rate of dihydrostreptomycin and tetracycline from the blood was studied in cats whose renal vessels and common bile ducts had been ligated to prevent excretion. The blood concentration curves showed that for each antibiotic the absorption from the blood had largely terminated 20—30 minutes after the injection. In cats the distribution-volume in the body was about three times greater for tetracycline than for dihydrostreptomycin.

Dihydrostreptomycin was found in high concentrations in the blood. It also accumulated in tissues of mesenchymal origin. The concentration of tetracycline on the other hand was lower in the blood than in any tissues with the exception of the central

* Paper read at the pharmacological meeting August 30th.

nervous system. It was high in lymphoid tissues and in the skeleton. After about five hours the greater part of each antibiotic had disappeared from the body.

A description is given, together with autoradiographic illustrations of the distribution of dihydrostreptomycin and tetracycline in different organs and tissues.

Asmussen, E. and M. Nielsen (Laboratory for Theory of Gymnastics and Zoophysiological Laboratory, University of Copenhagen, Denmark): MEASUREMENTS OF ARTERIAL pO_2 IN LIGHT AND HEAVY EXERCISE.

The present experiments which are a part of a more extensive study of the regulation of respiration and circulation during muscular exercise were undertaken in order to investigate if the arterial oxygen hypotension is more severe during heavy work than in light work.

The arterial oxygen tension was determined by a modification of KROGH's bubble method: an air bubble of about 50 mm^3 is equilibrated in 3 cc of anaerobically drawn arterial blood by rotation at 37° C for 15 to 20 min and then transferred to the micro-gasanalyzer and analyzed for CO_2 and O_2. 33 control experiments with blood of known O_2-tensions around 100 mm Hg showed that the oxygen tensions determined by this method were on an average 0.6 mm Hg too low with a standard deviation of ± 1.4 mm Hg.

Two series of work experiments, one light (11 experiments, corresponding to an O_2-uptake of about 1.8 l/min) and one heavy (12 experiments, corresponding to an O_2-uptake of about 3.3 l/min) were undertaken on a group of normal young men. It was found that the arterial pO_2 was 84 mm Hg (range 78—89) in light work and 86 mm Hg (range 82—91) in heavy work.

The experiments give no support to the assumption that a more severe arterial oxygen hypotension exists in heavy work than in light work.

Bárány, F. R. (S:t Eriks Hospital, IInd Medical Service, Stockholm, Sweden): ATTEMPTS TO DETERMINE THE SENSITIVITY OF THE PILOMOTOR MUSCLE TO NORADRENALINE IN MAN.

l-Noradrenaline bitartrate, dissolved in water, is introduced into the skin of the forearm by electrophoresis (iontophoresis). The lowest strength of current (i), producing visible gooseflesh within a given time, is determined.

The following factors have been studied:

1. The influence upon i of different concentrations of the noradrenaline solution. It is shown that i is fairly constant at concentrations from 1 to 250 μg/ml. (20 experiments in 8 subjects.)

2. The correlation between the minimum current required to produce gooseflesh and the time of electrophoresis. These factors are inversely and linearly correlated except at very short times (under 1½—2 min). (20 experiments in 8 subjects.)

3. The influence upon i of arterial occlusion (cuff around the upper arm). This results in a significant fall of i by 10.3 ± 4.0 % ($P < 0.01$). (65 experiments in 50 subjects).

4. The influence upon i of blocking cutaneous nerves to the forearm with xylocain (lignocain). This results in a significant rise of i by 14.3 ± 5.6 % ($P < 0.01$) within the anesthetic skin area. (28 experiments in 15 subjects.)

5. The influence upon i of indirectly induced vasodilatation. The left forearm and hand were immersed in hot water (+ 44° C) until sweating became visible in the right forearm ($\sim$ 20 min); i was determined in the right forearm before and after the heating. There was no significant change of i (decrease by 6.8 ± 8.4 %). The skin temperature was somewhat lower after the heating than before (difference 0.9 ± 0.2° C), probably due to the sweating. Room temperature $\sim$ 20° C. Relative humidity $\sim$ 50 %. (26 experiments in 26 subjects.)

6. The influence upon i of local heat applied to the skin. Moderate heating with hot air did not influence i (decrease by 4.5 ± 6.3 %; rise in skin temperature 2.0 ± 0.2° C). More intense heating for about 20 minutes with water at 44° C, which

resulted in a bright red skin, gave a probably significant decrease of i by 17.7 ± 8.1 % ($0.01 < P < 0.05$). Determinations of i and skin temperature readings were made before and 2—5 minutes after the heating. The skin temperature was 2.8 ± 0.2° C higher at the last reading than before the heating. — There seems to be no correlation between skin temperature and i neither before nor after the heating (r^{∞}—0.1 in both cases). — (25 experiments in 25 subjects.)

7. The correlation between the strengths of current necessary to produce gooseflesh and blanching of the skin respectively. Investigation in progress.

8. The correlation between blood pressure of the subject and i. Investigation in progress.

Berglund, E., H. Borst, F. Duff, R. Monroe and G. Schreiner (Department of Physiology, Harvard School of Public Health, Boston, Mass., USA): EFFECTS OF HEART RATE, CARDIAC STANDSTILL AND VENTRICULAR FIBRILLATION ON MYOCARDIAL OXYGEN CONSUMPTION AND CORONARY BLOOD FLOW IN THE DOG.

I. *Heart rate experiments:* Cardiac output and left main coronary artery inflow were continuously recorded (Circulation Research 1954. 2. 319) together with atrial and arterial pressures. Blood samples were obtained from aorta and coronary sinus. Myocardial oxygen consumption was estimated as the product of left coronary flow and A-V oxygen difference.

Heart rate was controlled by surgical production of A-V block and subsequent electrical stimulation of the ventricles. At each rate a wide range of ventricular work loads was examined.

When the rate was raised in steps from a level of 40—80 to above 200 per minute myocardial oxygen consumption increased. The ratio between left ventricular mechanical work and myocardial oxygen consumption decreased with increased rate. At comparable levels of ventricular minute work myo-

cardial oxygen consumption was 1.5—2.0 times as high at a rate of 180 as at 90 per minute. Coronary flow increased roughly in proportion to myocardial oxygen consumption.

II. *Cardiac standstill and ventricular fibrillation:* The left main coronary artery was perfused from a donor dog's carotid artery, and blood was returned into the donor dog's femoral veins from the right atrium. During standstill or fibrillation (up to 37 minutes) the aorta was perfused from the donor dog's femoral arteries. Pressures in left atrium, left ventricle, aorta and coronary arterial inflow tubing were recorded together with coronary artery flow. Myocardial oxygen consumption was estimated as described above.

Cardiac standstill was induced by intracoronary infusion of K-citrate, and ventricular fibrillation by electric shock. Control values were obtained before and after these procedures.

During cardiac standstill myocardial oxygen consumption fell to between 9 and 25 per cent of control values. During ventricular fibrillation it was 4 to 9 times as high as during standstill. Attempts were made, though not always successfully, to maintain a constant coronary perfusion pressure. Coronary blood flow during cardiac work, standstill and fibrillation varied in the same direction as myocardial oxygen consumption. In one experiment coronary A-V difference remained almost constant and the coronary flow was directly proportional to the oxygen consumption.

Myocardial oxygen consumption increases with increased heart rate, is low during cardiac standstill, and high during ventricular fibrillation. It is a major determinant of coronary blood flow.

Bergström, L. and R. M. Bergström (Aus dem Physiologischen Institut der Universität, Helsinki, Finnland): AKTIONSPOTENTIALABLEITUNG VOM WEHENDEN MENSCHLICHEN UTERUS.

Gemäss STEER und HERTSCH (1950) sowie HERTSCH (1954) ergibt sich beim Ableiten der Aktionspotential-

schwankungen (mittels Plattenelektroden, die auf der Bauchdecke belegen sind) vom wehenden menschlichen Uterus »sinusoidale» Kurven mit einer Frequenz von 1/3—2 Hz (20—120/Min). Vom Jahre 1955 teilt SIENER mit, dass er vom nichtschwangeren Uterus Ekg-, atem- und pulssynchrone Kurven erhalten hat, die er für extrauterine Störungen hielt.

In unseren Untersuchungen, die mit Kreissenden vorgeführt wurden, erhielten wir gleich wie STEER und HERTSCH »sinusoidale» Potentialschwankungen, deren Frequenz zwischen 16—28/Min variierte, und zwar kamen sie regelmässig auch zwischen den Wehen atemsynchron vor. Eine vollständige Ausschaltung der Atmung während der Wehe konnte unseres Erachtens von der Versuchsperson nicht durchgeführt werden.

Das Ergebnis gibt Anlass zu der Vermutung, dass bei der klinischen Bewertung des Elektrouterogramms (der in obengenannter Weise erhalten ist) zwecks Beurteilung der Wehentätigkeit im schwangeren Uterus die extrauterinen Störungen, insbesondere die von der Atmung herrührenden, mitzuberücksichtigen sind.

Hertsch, G. J., Amer. J. Obst. & Gynec. 1954. *68*. 867.
Siener, H., Arch. Gynäk. 1955. *185*. 581.
Steer, C. M. und G. J. Hertsch, Amer. J. Obst. & Gynec. 1950. *59*. 25.

Bergström, R. M. (Aus dem Physiologischen Institut der Universität, Helsinki, Finnland): DIE PERIODENZAHL DES ELEKTROMYOGRAMMS ALS BEGRIFFSABBILD DES ERLEBNISSES EINER VOLUNTÄREN MUSKELAKTION.

Die begriffliche Abbildung (Reizbeschreibung) der Erlebnisse der Muskelspannung gelingt mittels des Produkts der vom Muskel entwickelten, physikalischen Kraft und ihrer Wirkungsdauer (RENQVIST 1930). Andererseits herrscht unter gleichen Versuchsbedingungen eine lineare Beziehung zwischen dieser Kraft und der motorischen Impulsfrequenz des Elektromyogramms (JALAVISTO, LIUKKONEN, REENPÄÄ und WILSKA 1938).

Gemäss dieser Befunde wird die Frage gestellt, ob nicht der Begriff der Kraft im obigen Reizausdruck durch den Begriff der Frequenz zu ersetzen ist.

Es wurden zu diesem Zweck topologische Messungen im Bereich der Erlebnisse der Aktivbewegungen (m. interosseus dors. I) ausgeführt, wobei die Aktionspotentiale des Muskels registriert wurden. Die Ergebnisse zeigten, dass das Produkt der genannten Frequenz und deren »Wirkungsdauer» die Topologie wiedergibt, d.h. die Erlebnismannigfaltigkeit der voluntären Muskelaktion ist mittels der Begrifflichkeit der Gesamtzahl der EMG-Impulse bei der Muskelaktion abbildbar. Es wird die Bedeutung des Ergebnisses behandelt.

Jalavisto, E., L. Liukkonen, Y. Reenpää und A. Wilska, Skandinav. Arch. f. Physiol. 1938. 79. 39.
Renqvist, Y., Skandinav. Arch. f. Physiol. 1930. 59. 53.

Bertler, Å., A. Carlsson, J. Nilsson and E. Rosengren (Institute of Pharmacology, University of Lund, Sweden): EFFECT OF RESERPINE ON THE METABOLISM OF CATECHOL AMINES.

The disappearance of catechol amines (adrenaline and noradrenaline) from the adrenal medullas (CARLSSON and HILLARP 1956) and from the hearts (BERTLER, CARLSSON and ROSENGREN 1956) of rabbits given reserpine prompted us to a more detailed study of the effect of this drug on the metabolism of catechol amines. In the present experiments on rabbits the catechol amine content of brain, heart and adrenals was studied at varying times after intravenous injection of varying doses of reserpine. In some experiments the urinary excretion of adrenaline and noradrenaline was investigated. Perfusion experiments on isolated organs have also been done. Some results are summarized below.

1. The heart is extremely sensitive to reserpine. Within 16 hours 0.005 mg per kg bodyweight of the drug causes a very marked drop in the catechol amines of the heart. The brain is somewhat less sensitive while the adrenal medulla is rel-

atively resistent and requires a dose of about 1 mg per kg for a comparable effect. Denervation or section of the spinal cord at C_6 makes the adrenal medulla even less sensitive.

2. After a large dose of reserpine (5 mg per kg bodyweight) the disappearance of catechol amines from the brain is almost complete in 1 hour. The corresponding intervals for heart and adrenals are 3 and 16 hours, respectively. The return to normal values requires about a month in the brain and 2 weeks in the heart and adrenals.

3. In brain and adrenals but not in heart the drop in catechol amines caused by reserpine is largely prevented by marsilid pretreatment.

4. Owing to lack of the adrenergic transmitter the reserpinized organism fails to show the usual blood pressure response to stimulation of the sympathetic nerves, as demonstrated in experiments on cats. Presumably a similar mechanism is operating in the central part of the adrenergic system.

5. The evidence so far available suggests a similar mechanism of action of reserpine on the catechol amines as on serotonin. It would appear that lack of rather than an excess in free form of biogenic amines should be considered as the cause of some of the pharmacodynamic effects of reserpine.

Bertler, A., A. Carlsson and E. Rosengren, Naturwissenschaften. 1956. *43*. 521.

Carlsson, A. and N. Å. Hillarp, Kungl. Fysiogr. Sällsk. Lund Förh. 1956. *26*. Nr 8.

Bojesen, E. and J. Egense (Institute of Medical Physiology, University of Copenhagen, Denmark): LACK OF UTILISATION OF CORTICOSTEROIDS (17-HYDROXY-CORTICOSTERONE AND CORTICOSTERONE) IN EXTRAHEPATIC TISSUES.

Using a previously described analysis for specific determination of corticosteroids in plasma and tissues (BOJESEN 1956) the breakdown of these hormones at normal levels of concentrations in extrahepatic tissues has been studied. The following preparations have been used: *1*) eviscerated and

adrenalectomised cats, 2) artificially perfused hindlimbs of cats and dogs, 3) artificially perfused brains of dogs. It has been found that without the liver no breakdown or fixation of free corticosteroids occurred during experimental periods of several hours. The same has been found in the isolated hindlimb preparation during electrically induced work.

These data will be discussed in relation to current theories about the working mechanism of the corticosteroids.

Bojesen, E., Scand. J. Clin. & Lab. Invest. 1956. *8*. 55.

Buchthal, F. and L. Engbæk (Institute of Neurophysiology, University of Copenhagen, Denmark): PROPAGATION VELOCITY OF INTRACELLULARLY RECORDED ACTION POTENTIALS IN STRIATED FROG MUSCLE FIBRES.

Single muscle fibres were stimulated directly *in situ* by an intracellular electrode and the arrival time of the action potential was recorded intracellularly in three or four points along the fibre. Large fibres were selected on the surface of the sartorius muscle since they could be identified over a distance of 8 to 10 mm. The determination of propagation velocity requires a rectilinear relationship between arrival times of the action potential and distance of the points of recording from the point of stimulation. Experiments were discarded in which there were deviations from rectilinearity corresponding to differences in velocity between the different points of more than 0.25 m per sec. The propagation velocity was in the range of 1.9 to 3.4 m per sec (20° C). The point of stimulation and the position of the stimulating electrode did not coincide. Extrapolating the plot of arrival time of the action potential as a function of the distance from the stimulating electrode to zero time indicates that the propagated response started at a distance of maximally ± 1 mm from the stimulating electrode. Reducing the strength of stimulation to threshold caused an increase in arrival times of the action potentials. This increment can either be due to a displacement of the point

of stimulation to larger distances from the recording electrodes or to a delay in the initiation of the action potential of the order of 0.4 msec. The results will be discussed in relation to findings on isolated fibres and fibres of mammalian muscle.

Buchthal, F. and U. Jahn (Institute of Neurophysiology, University of Copenhagen, Denmark): SPONTANEOUS ACTIVITY IN ISOLATED MUSCLE SPINDLES.

Microscopical observations: In the isolated muscle spindle of frog's striated muscle (extensor longus dig. quart.) spontaneous contractions of single intrafusal fibres occurred at a frequency of 0.5—1 per sec (20° C) even in the absence of external tension. More rarely all two to three intrafusal fibres within the spindle contracted synchronously (frequency at maximum 0.5 per sec, 20° C). This spontaneous activity was also observed with the spindle *in situ* in the excised muscle and in the muscle *in situ* with intact nerve and vascular supply.

Electrical responses: Two types of electrical responses have been recorded in the relaxed isolated muscle spindle. One (*a*) is recordable from within the spindle along its entire length. These discharges are not accompanied by an action potential in the afferent nerve and are considered to be the action potentials of the intrafusal fibres. The other type of response (*b*) is confined to the equatorial region of the muscle spindle where the sensory spirals are located and is associated with an action potential in the afferent nerve. These responses probably represent the discharges from the sensory endings.

To record these potentials *either* 0.1—0.3 μ capillary microelectrodes were used penetrating the connective tissue sheath of the spindle immersed in Ringer's solution *or* 50 μ platinum electrodes leading off from the outside of the connective tissue sheath with the spindle immersed in mineral oil.

a) The action potential of the intrafusal fibre occurred at the same frequency as the visible contractions. It was diphasic with an initial positive deflection. When the electrode was

stepwise withdrawn from the point of maximum response (1.5 mV peak-to-peak for single fibre response, 3—5 mV for synchronous response) the action potential amplitude decreased 30 to 50 per cent before the electrode left the connective tissue sheath.

The action potential of the intrafusal fibres was propagated both in the polar regions and »transequatorially» as evidenced by simultaneous recording from two points within the spindle, the conduction velocity being 0.3 m per sec (20° C). This velocity fits the linear relationship between conduction velocity and fibre diameter found by HÅKANSSON (1956) for ordinary muscle fibres.

b) The type »*a*» response originating from the intrafusal muscle fibres was invariably succeeded by a response recordable only within the equatorial zone. The time interval between these two responses was 11 to 25 msec in the case of potentials from single intrafusal fibres, 6 to 11 msec in the case of synchronized responses from all intrafusal fibres either spontaneously occurring or evoked by electrical stimulation of the small efferents. Twenty to thirty msec after this discharge of the sensory spiral a new action potential was recorded from it and ten to twenty further discharges occurred before the next action potential of the intrafusal fibres. The discharges confined to the equatorial zone could be recorded wherever parts of the sensory spirals or the intrafusal sensory nerve were visible. They had frequently a steep negative onset or, if there was an initial positive phase, the following positive-negative deflection was of shorter duration than in the action potentials of the intrafusal muscle fibres. Maximum amplitude (1—2 mV) was recorded at once, when the electrode had pierced the connective tissue sheath and changed less with further advancement of the electrode in depth than did the potential of the intrafusal fibres. The »*b*» type potential could be recorded simultaneously from within and outside the structure which generates it. The amplitude of the internal positive potentials was 10 to 45 mV. In addition, at internal recording, fractional discharges of 1—3 mV were observed, not visible with external recording.

d-Tubocurarine (5 μg per ml) abolished reversibly the spontaneous contractions and potentials from the intrafusal fibres as well as the spontaneous discharges from the sensory spirals.

Håkansson, C. H., Acta Physiol. Scand. 1956. 37. 14.

Bugge-Asperheim, B. and K. Lange Andersen (Institute of Aviation Medicine, Royal Norwegian Air Force, Oslo, Norway): REDUCTION IN CO_2 STORES OF MAN DUE TO MUSCULAR EXERCISE.

The respiratory recovery from exercise has been studied using a spirometer of the closed circuit type which gives a continuous recording of the gas exchange.

It is demonstrated that bicycling 1500 kgm in 1 min leads to an increased lactic acid content of circulating blood which is followed by an excess blowing-off of CO_2 in the first minutes of recovery, amounting to 1—2 % of the estimated total CO_2 stores of the body.

No or only a slight tendency to CO_2-retention was observed during a two hours' post-exercise period, in which the gas exchange was recorded continuously.

***Campbell, D.** (Institute of Pharmacology, University of Uppsala, Sweden): TUBULAR SECRETION AND DIURETIC ACTION OF MERCURIAL DIURETICS.

Utilizing the renal portal circulation technique described by LINDAHL and SPERBER (1956) in chicken we have been able to study the renal excretion of nine different mercurial diuretics. Seven of these show clearly signs of tubular secretion. The rate of excretion of the different diuretics is very different, the biological halflife of an intravenous dose varying from 15 minutes to 200 minutes. With suitable doses a water diuresis can be obtained with all the diuretics tested. In the case of some diuretics, injection into a leg vein gives a strictly unilateral

* Paper read at the pharmacological meeting August 30th.

diuresis, higher doses give a bilateral diuresis and still higher give complete anuria. The water diuresis in these cases is accompanied by diuresis of Na and Cl; K seems to decrease. Various drugs interfering with the secretion of the diuretics also interfere with their diuretic action.

Lindahl, K. M. and J. Sperber, Acta Physiol. Scand. 1956. *36*. 13.

Carlsen, F. and G. G. Knappeis (Institute of Neurophysiology and Laboratory of Biophysics, University of Copenhagen, Denmark): ELECTRON MICROSCOPY OF ULTRATHIN LONGITUDINAL SECTIONS FROM STRIATED MUSCLE.

Electron micrographs of ultrathin longitudinal sections of striated muscle fibrils prepared from small bundles of frog's semitendinosus muscle showed two types of filaments (*A* and *I*). This is in agreement with previous observations on transverse sections (HUXLEY and HANSON 1954): The *I* filaments terminated within the *A* band. The zone at which the *A* and *I* filaments overlapped extended over 0.5 μ in the sarcomere at equilibrium length decreasing rectilinearly with increasing stretch (20 per cent per 10 per cent stretch). During isometric contraction the *A* and *I* filaments overlapped less than in the resting fibre, the overlap being 0.3 μ at equilibrium length. At a sarcomere length of about 3.0 μ corresponding to 35 per cent of stretch there was no longer any overlap in the resting or in the isometrically contracted fibril. During isotonic contraction the overlap between the *A* and *I* filaments increased to such a degree that the *I* filaments seemed to pass uninterrupted throughout the entire length of the sarcomere. The transverse spacing between the *A* filaments was up to 25 per cent larger in the isotonically contracted fibril than at rest.

The width of the interspaces between the fibrils occupied by the sarcoplasmic reticulum averaged in the resting and isometrically contracted fibre 0.04 μ. During isotonic contraction the width increased to an average value of 0.13 μ.

Huxley, H. E. and J. Hanson, Nature, London, 1954. *173*. 973.

Carlsten, A. and G. Grimby (Department of Clinical Physiology, University of Gothenburg, Sweden): THERMAL GRADIENTS BETWEEN RECTUM, ESOPHAGUS AND RIGHT HEART BLOOD IN MAN.

Blood in the right heart is a mixture of blood from peripheral and central parts of the body (the core) with warm blood especially from the liver and kidney. At rest the temperature of the heart blood is fairly constant and somewhat lower than the rectal temperature. The temperature in the lower esophagus proved to be a good index of the heart blood temperature in man.

With procedures resulting in a decreased blood flow from the periphery to the heart (pooling of blood in the lower limbs) the temperature in the right auricle slightly increases. Pooled blood leaving the leg after venous and arterial occlusion is cooled as measured in the femoral vein. After release of this blood pool the temperature of the heart blood and esophagus decreases, in contrast to an almost constant rectal temperature.

After immersion in cold or warm water of the legs containing pooled blood, the heart blood temperature rapidly falls when the circulation is released. The duration of this temperature fall is longer after immersion in warm water than in cold.

In warm and cold baths, there is a more rapid reaction of the temperature in the esophagus than in the rectum, resulting in large thermal gradients.

Clemedson, C.-J., T. Fredriksson and B. Sörbo (Research Institute of National Defence, Sundbyberg, Sweden): BIOCHEMICAL AND PHARMACOLOGICAL STUDIES ON SODIUM MONOTHIOPHOSPHATE.

Sodium monothiophosphate, when incubated with rat liver homogenates under aerobic conditions, is in part converted to thiosulfate. This reaction involves an enzymic hydrolysis of thiophosphate to hydrogen sulfide and phosphate (BINKLEY 1949) followed by a non-enzymic oxidation of hydrogen sulfide

according to a previously established mechanism (SÖRBO 1956). Monothiophosphate can replace orthophosphate in the phosphoglyceraldehyde dehydrogenase reaction; an unstable intermediate is however formed. The ability of thiophosphate to replace orthophosphate in other enzymic phosphorylation systems was also investigated.

The acute toxicity of sodium monothiophosphate as tested by intraperitoneal injection in albino mice was found to be 0.95 g per kg bodyweight. The animals had slight convulsions, and the respiration was deep and slow. After intravenous injection in the anaesthetized cat even low doses (less than 500 mg per kg bodyweight) resulted in depression of the respiration and fall of the blood pressure. Higher doses gave prolonged apnea, considerable fall of the blood pressure and standstill of the heart. Even at these high doses the neuromuscular transmission was unaltered. The effect of the thiophosphate on blood pressure and respiration was compared with that of hydrogen sulfide, which compound, however, had an initial stimulating effect on the respiration and also gave elevation of the blood pressure.

Binkley, F., J. Biol. Chem. 1949. *181*. 317.
Sörbo, B., Biochim. et Biophys. Acta 1956. *21*. 393.

Clemedson, C.-J., H. Hartelius and G. Holmberg (Research Institute of National Defence, Sundbyberg, and King Gustaf V:s Research Institute, Stockholm, Sweden): CARBON DIOXIDE AND THE BLOOD-BRAIN BARRIER.

The effect on the blood-brain barrier of inhalation of 7.5 to 30 per cent carbon dioxide in oxygen has been studied in rabbits, guinea-pigs and cats. The trypan blue test was used to demonstrate increased capillary permeability and also small hemorrhages were observed as a sign of capillary damage.

In rabbits significant blue stainings occurred within 3—4 min of 30 per cent CO_2, 5—15 min of 20 per cent, 20—30 min of 15 per cent, 30—60 min of 10 per cent but not within one hour of 7.5 per cent CO_2. The appearance of hemorrhages

varied along similar but not quite parallel lines. This was true when the dye injection had been made before the gas exposure. On the other hand, dye injection a few minutes after the exposure revealed little residual damage, which indicates that the increase in capillary permeability is mainly of a reversible kind. The hemorrhages were still equally frequent.

The changes, which were sometimes of a maximal degree, were mainly concentrated to the brain stem and cerebellum but scattered changes were seen in all parts of the brain; in the spinal cord blue staining never occurred.

The results of the guinea-pig experiments were very similar to those of the rabbit experiments, while in cats the changes were less pronounced indicating a greater resistance of the capillary walls.

There is a striking resemblance between these effects of CO_2 and the effects of electrically induced convulsions shown by BJERNER, BROMAN and SWENSSON (1944), and it is possible that also the latter effects may be due to an excess of CO_2 in the brain.

Further experiments on the effect of CO_2 on the distribution of certain drugs in the CNS are going on.

Bjerner, B., T. Broman and Å. Swensson, Acta psychiat. et neurol. 1944. *19*. 431.

Clemedson, C.-J. and H. Hultman (Research Institute of National Defence, Sundbyberg, Sweden): EFFECTS OF HIGH EXPLOSIVE AIR SHOCK WAVES ON THE PERFORMANCE OF THE HEART IN RABBITS.

The rapid shallow breathing and bradycardia observed in experimental animals immediately after exposure to a detonating high explosive charge and reported in earlier publications (KROHN, WHITTERIDGE and ZUCKERMAN 1942, CLEMEDSON 1949, BENZINGER 1950 and CLEMEDSON and PETTERSSON 1953) have been interpreted as being due to vagal reflexes elicited essentially in the damaged lungs.

If the animals have been deprived of their pulmonary vagal innervation by intrathoracal denervation before the exposure, the respiration remains normal after the detonation. The innervation of the heart is maintained and in these animals the heart rate decreases to the same extent as in the non-denervated animals, indicating that the impulses causing the bradycardia are of extrapulmonary origin. Microscopically observable lesions in the myocardium suggest that the origin might be found within the heart itself. These findings, as well as the question of the immediate cause of death, also initiated a study of the working efficiency of the blast injured heart.

The output of the heart, determined by means of the direct Fick method, is decreased within a few minutes after the detonation even in surviving animals, the decrease showing a close correlation to the weight of charge used, *i.e.* to the force of the shock wave. In severe exposure with eventually lethal injuries the output per minute is often reduced to 10 to 20 per cent of the pre-exposure value. The decrease may be due in part to a diminished return from the damaged lungs, but the correlation of the cardiac output to the lung injury is less than to the weight of charge used. The significance of this fact for the fatal outcome in animals with only moderate lung injuries will be discussed.

Benzinger, T., German Aviation Medicine. World War II. U.S. Govt Printing Office, Washington D.C. 1950. II: Ch.XIV-B. 1225.
Clemedson, C.-J., Acta Physiol. Scand. 1949. *18*. Suppl. 61.
Clemedson, C.-J. and H. Pettersson, Am. J. Physiol. 1953. *174*. 316.
Krohn, P. L., D. Whitteridge and S. Zuckerman, Lancet 1942. *1*. 252.

Diamant, B., B. Högberg, I.-L. Thon and B. Uvnäs (Department of Pharmacology, Karolinska Institutet, Stockholm, and AB Leo, Helsingborg, Sweden): HISTAMINE RELEASE AND MAST CELL »FRAGMENTATION» PRODUCED BY AN AGENT ISOLATED FROM ASCARIS LUMBRICOIDES.

Crude extracts of Ascaris produce a shock-like syndrome when given intravenously to dogs (RICHET 1905). The hista-

mine level in the blood increases (ROCHA E SILVA and GRAÑA 1946). We have attempted to isolate a histamine releasing principle from extracts of Ascaris lumbricoides (eelworm from swine). As a measure of the activity of the preparations was used their ability to »disrupt» mast cells from the rat mesentery and to release histamine from the perfused cat's paw.

An active material was prepared by extracting the worms in ethanol, dialyzing the alcohol soluble material and purifying the non-dialyzable fraction by means of a resin column (XE 64). The activity of the preparations obtained compared favourably with 48/80. The biological and chemical properties of the preparation will be discussed.

Diamant, H. and B. Holmstedt (The Ear, Nose and Throat Department, Karolinska Sjukhuset, and Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): **INTRAVENOUS INFUSION OF ACETYL-BETA-METHYLCHOLINE IODIDE (MeCh) AND THE EFFECT OF ATROPINE.**

The experiments which will be described here have been undertaken for several reasons.

1. To get reliable data on the volume and rate of secretion of saliva under normal and pathological conditions.

2. To study the effect of acetyl-β-methylcholine iodide (in the following referred to as MeCh) in humans.

3. To study the effect of antidotes, especially atropine, on the symptoms provoked by MeCh, which in turn aroused the interest in the way drugs are absorbed when various routes of administration are used.

We have found that MeCh can be given intravenously without any untoward effects. It is necessary to have an objective recording of the symptoms. The description of our method has been given in Arch. Int. Pharmacodyn. (in press).

The injections of MeCh have been given in periods of 5 minutes. Salivation, blood pressure and pulse rate have been recorded quantitatively. There is an almost linear dose response curve for salivary secretion.

MeCh infusions mimic all the muscarine-like symptoms of poisoning with organophosphorous cholinesterase inhibitors.

Atropine sulphate has been used to counteract these symptoms. An intravenous injection of 0.25 mg atropine causes a decrease in salivation in about thirty seconds, but it takes about one minute for complete arrest of all the symptoms.

The rapidity of onset of the antidote effect is important when atropine and other remedies are used to counteract the effects of the very quickly acting organophosphorous compounds. An intravenous injection of atropine is, for practical reasons, ordinarily out of the question. The intramuscular way is suggested by many as the next best. In view of the importance of the necessity of quick action of the antidotes, we have studied different ways of administration. First of all the comparative effects of subcutaneous and intramuscular injections were examined.

When intramuscular and subcutaneous injections are compared in the same subject we have found in most cases that absorption takes place more quickly after subcutaneous than after intramuscular injection. The absorption of the subcutaneously deposited fluid depends on many factors, like the site of the injection, the thickness of subcutaneous fat, the kind of injector used, not to mention well-known factors like concentration of the injected substance and volume of the injected solution.

Our results have shown that the intramuscular route is not always the fastest way of administering antidotes.

Döbeln, W. von (Department of Physiology, Kungliga Gymnastiska Centralinstitutet, Stockholm, Sweden): THE PHYSIOLOGICAL IMPORTANCE OF THE FORCES OF INERTIA IN THE ANIMAL ORGANISM.

Dyrberg, V. and W. Hougs (The Anaesthesia Laboratory, Copenhagen County Hospital, Gentofte, and the Research Laboratory of GEA, Ltd., Copenhagen, Denmark): CHLORPROMAZINE AND NEUROMUSCULAR BLOCKING AGENTS.

Contradictory accounts have been given in the literature of the effect of chlorpromazine alone and the interaction of this substance and the neuromuscular blocking agents.

The results of a previous series of experiments (presented at the Annual Meeting of the Scandinavian Society of Pharmacologists, Copenhagen, August 1955) in which chlorpromazine was given to cats during the restoration phase after single doses of neuromuscular blocking agents and during continuous infusion of these drugs, suggested that chlorpromazine intensifies the effect of non-depolarizing substances and counteracts that of depolarizing substances on the anterior tibial muscle, which is »white». In the present paper we present the results of supplementary experiments in cats with the anterior tibial muscle (»white»), the soleus muscle (»red») and the gastrocnemius muscle (»mixed»).

The contractions of the exposed anterior tibial muscle, the soleus and the gastrocnemius muscles were recorded kymographically during indirect stimulation of the cut sciatic nerve.

The results of the experiments showed that chlorpromazine intensifies the effect of d-tubocurarine, gallamonium, and benzoquinonium, whereas it reduces the effect of decamethonium and succinylcholine on the different muscle types.

The interaction of chlorpromazine and the neuromuscular blocking agents is discussed, and the conclusion is drawn that an anti-acetylcholine activity of chlorpromazine is the most likely explanation of our findings.

Edgren, B. (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): STUDIES IN THE CLEARING OF PLASMA AFTER INTRAVENOUS ADMINISTRATION OF FAT EMULSIONS.

Two types of fat emulsion were given intravenously to

dogs and the plasma content of optically visible fat was estimated turbidimetrically.

The fat emulsions contained 25 per cent cottonseed oil. One type of emulsion contained polypropylenethylenglycol (Pduronic F 68) as emulsifying agent besides phosphatides, and the other type contained glycerin monostearate and sodium cholate as emulsifying and stabilizing agents together with purified soybean phosphatides.

The emulsions were administered intravenously to dogs in amounts ranging from 2.5 to 7.5 g of neutral fat per kg bodyweight, and the clearing of plasma was followed turbidimetrically.

It was found *1*) that the disappearance of plasma turbidity after intravenous administration of fat emulsion followed an exponential curve, and *2*) that the rate of clearing decreased when the dose of administered fat was increased, *i. e.*, the clearing activity varied inversely with the dose.

Edman, K. A. P. (Institute of Pharmacology, University of Uppsala, Sweden): REVERSIBLE RELAXATION OF GLYCERIN-EXTRACTED MUSCLE FIBERS BY METAL IONS IN THE PRESENCE OF ATP.

In a recent paper (EDMAN 1956) a relaxing effect on glycerin-extracted psoas fibers by zinc and calcium was described. The minimum bath concentration of zinc for complete relaxation of contracted fibers is as low as 5×10^{-5} M. Several other bivalent metal ions have similar effect, but in much higher concentrations in the bath. The implications of these findings are discussed.

Edman, K. A. P., Acta Soc. Med. Upsal. 1956. *61*. 215.

Egense, J. (Institute of Medical Physiology, University of Copenhagen, Denmark): ARTIFICIAL PERFUSION OF ISOLATED DOG BRAIN (EFFECT OF INSULIN ON GLUCOSE AND POTASSIUM).

A technique for perfusion of the isolated dog brain has been worked out. With a few unimportant exceptions, all vessels to extracerebral tissue are ligated. The branches from aa. carotis communes, aa. carotis externae, vv. jugulares externae and vv. jugulares internae (if present) are isolated and ligated. A special clamp across epistropheus compresses aa. vertebrales and medulla spinalis including a. spinalis dorsi and sinus venosus vertebralis. The brain is then only irrigated through aa. carotis internae, aa. ophthalmicae with their important rami anastomotici to the brain and vv. cerebrales superiores; the latter are drained by vv. jugulares externae. The head is completely separated from the rest of the body and cannulae are inserted in aa. carotis communes and vv. jugulares externae. The preparation is connected to a perfusion pump (slightly modified), which has been used for several years at this institute. Nembutal narcosis has been used, sometimes with supplementary $N_2O + O_2$. The perfusion blood is taken from a donor dog in ether-narcosis and defibrinated. Glucose 5—10 % is injected during the perfusion.

The following values have been obtained in the best experiments per 100 g brain (wet):

Blood flow per minute	46 ml
Oxygen consumption	2.4 ml per minute
Glucose consumption	3.0 mg per minute

The blood pressure was 60—225 mm Hg.

During most of the experiments lactic acid was determined and the values found were between 33 to 60 mg %, with no regular tendency to increase or decrease.

In the last four experiments a single dose of insulin was injected after a steady state had presumably been reached in the blood. The values of the blood sugar during the following 15—30 minutes remained unaltered or continued to fall at

an unaltered rate if the fall started in the period before the insulin injection. Simultaneous determinations of potassium and sodium in plasma also showed unchanged values.

For comparison hindlimb perfusions were carried out on dogs and cats which showed a distinct fall in blood sugar and potassium within the same period, as expected.

These preliminary experiments presumably show that insulin has no effect on the glucose metabolism in the brain and neither does it affect the potassium level there. From these experiments it is impossible to say anything about the exact mechanism. Two possibilities will be discussed: *1*) insulin does not pass the blood-brain barrier; *2*) insulin does not affect the uptake of glucose into the brain cells.

Enger, P. S. and J. Steen (Institute of Zoophysiology, University of Oslo, Norway): CALORIC SIGNIFICANCE OF INVISIBLE MUSCLE ACTIVITY DURING COLD STRESS.

Pigeons were exposed to different air temperatures ranging from + 20° to — 22° C. Thermocouples were inserted in the abdomen, pectoral muscles and under the breast skin. At — 22° C the pectorals stayed 1—2° warmer than the abdomen, the temperature of which remained more or less constant. The gradient disappeared gradually with rising temperature, and at + 20° abdominal and pectoral temperatures were the same. Also subcutaneous temperatures over the pectorals were higher during the cold. Myograms recorded from the pectorals at — 22° C showed a considerable electrical activity which decreased with increasing air temperature, and nearly vanished at + 20° C. Below the critical temperature, + 13° C, the metabolism increased linearly with falling temperature, which indicates that the overall insulation remained about constant at its maximal value. The rising temperature in the pectoral muscles with lowering of the subcritical air temperature must therefore be due to an increased heat production in the muscles. The increasing myographic activity with lowering of the temperature indicates that the heat production is caused

by invisible muscle activity. Considering that the pectoral muscles of a pigeon constitute some 30 % of the total body-weight it is clear that heat production in these muscles will contribute very considerably to the elevated metabolism in the cold.

Eriksen, L. (Institute of Medical Biochemistry and Physiology, University of Oslo, Norway): A STUDY OF THE BIOSYNTHESIS OF HEMOGLOBIN BY RABBIT RETICULOCYTES IN VITRO.

Erikson, G. and H. Erikson (The University Institute for Respiratory Physiology, Ullevål Hospital, Oslo, Norway): RESTING METABOLISM IN RELATION TO PREDICTED BASAL METABOLISM.

The resting ventilation, oxygen uptake and carbon dioxide output have been determined twice on each of 56 subjects (hospital patients) with an interval of a few days between determinations.

The determinations were done between 9 a.m. and 2 p.m. The subjects had all had breakfast at 7.30 a.m. and the patients examined after 12 o'clock in addition had received some soup at 11 a.m. None of the patients suffered from metabolic disturbances. Sedative drugs were not used before the examination. The resting metabolism was determined while the subject was seated in a comfortable chair.

The time required for obtaining resting values is shown. Expressed in per cent of predicted basal metabolism the mean value for the first set of determinations was 106 per cent (range: 134 to 78 per cent), and for the second set of determinations 103 per cent (range: 125 to 82 per cent).

These data show that practically basal values can be obtained without the rather rigid conditions generally used.

Erikson, H. (The University Institute for Respiratory Physiology, Ullevål Hospital, Oslo, Norway): THE RESPIRATORY RESPONSE TO ACUTE EXERCISE OF ESKIMOES AND WHITES.

The respiratory gaseous exchange of 10 Alaskan male eskimoes and 10 white male subjects during rest and during and after a work performance of approximately 1125 kgm in the course of 1 minute on a bicycle ergometer was determined.

During rest the only difference between the two groups of subjects was that the eskimoes had a higher resting metabolism. The difference in this limited material might be accidental, or can also be due to the fact that the eskimoes under these circumstances were more tense than the whites.

The work efficiency of the eskimoes, who never had bicycled before, was almost the same as that of the whites, who were all used to bicycling.

The eskimoes, who were shorter and lighter than the white subjects, had a shorter recovery time indicating a better cardiorespiratory function. For types of exercise which are a function of the bodyweight, the difference would have been even more pronounced.

Euler, C. von and J. D. Green (Department of Anatomy U. C. L. A. and V. A. Hospital, Long Beach, Calif., USA): THE ROLE OF DENDRITES IN HIPPOCAMPAL SEIZURES.

A postsynaptic potential may be recorded from the pyramidal cells of Ammon's horn after stimulation of the fornix. It is not transmitted through the alveus and depends on deeper afferents. Extracellular microelectrodes indicate depolarisation at and just below the cell layer. During repetitive stimulation the area of depolarisation involves the apical dendrites to progressively greater extents. When an inward current is demonstrable in the distal parts of the apical dendrites, seizure

discharges or driven seizure spikes occur. There are indications that spread may occur across damaged areas by ephapsis through artificial synapses and possibly such spread may occur between dendrites also in propagation through undamaged tissues. During seizure discharges a DC potential is developed between the dendritic layers above and below the pyramidal cellbodies, but its magnitude is probably not great enough to sustain a discharge.

Euler, C. von and U. Söderberg (Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden): ON THE SETTING OF THE BODY THERMOSTATE.

In lightly anaesthetized cats and rabbits the threshold temperatures for several temperature regulating reactions, *i.e.*, onset and cessation of shivering and cutaneous vasoconstriction were repeatedly determined when stimulating the animals in various ways.

It was found that various stimuli, such as nociceptive stimulation, pinna reflex and electrical stimulation of the midbrain tegmentum which all activated the electroencephalogram and the gamma motor system tended to raise the temperatures at which both heat-producing and heat-dissipating reflexes are brought into action, with a rise in body temperature as a consequence.

Similar shifts of the temperature for thermal balance were obtained by systemic infusion of adrenaline and noradrenaline. Changing the composition of the inspired gas was also found to influence thermoregulation.

Stimuli which inhibited the activity of the gamma motor system and evoked a synchronized cortical activity, *e.g.*, stroking the back of the animal, lowered the threshold temperatures with a slight fall in body temperature as a result.

The results support the view that the body temperature is set at different levels in different states of activity.

Euler, U. S. von and F. Lishajko (Department of Physiology, Karolinska Institutet, Stockholm, Sweden): INTRAAXONAL STATE AND STORAGE OF THE ADRENERGIC NERVE TRANSMITTER.

It has been suggested that the adrenergic nerve transmitter is synthesized and stored in specific structural units in the axones (EULER 1954). This concept is partly based on the fact that the transmitter is accumulated in the peripheral parts of the axone as evidenced by the ratio of the noradrenaline content in the splenic nerve trunk and the spleen (5:1). Moreover, the inexhaustibility of adrenergic transmitter release on stimulation seems to exclude repletion of the stores by axoplasm flow and suggests local resynthesis.

In support of this concept it has been shown that a submicroscopical sediment rich in noradrenaline is obtained by centrifugation of homogenized beef splenic nerves or spleen tissue (EULER and HILLARP 1956). While the nerve homogenate contains histamine and noradrenaline in the proportion 5—10:1 the sediment obtained by centrifugation at about 10 000×g for 1 hour contains noradrenaline in a concentration 10—30 times that of the homogenate but no histamine (EULER 1956).

Further experiments have shown that centrifugation of homogenates of splenic nerves of the ox in 0.45 M sucrose or isotonic saline yields a sediment which is biologically inactive when suspended in isotonic neutral solution but becomes highly active after addition of acid to pH 3—4. By column chromatography noradrenaline and a small amount of dihydroxyphenylacetic acid can be demonstrated, but no dopamine.

After removal of cell débris and nuclei by centrifugation for 5 min at 3 000×g, about 70 p.c. of the total activity in the supernatant occurs in a biologically active form. By addition of acid to the supernatant the remaining 30 p.c. of the total activity is released. After separation of the active sediment no further activity can be released by addition of acid to the supernatant.

It is concluded that the transmitter is stored in high con-

centration in structural units which may be sedimented by centrifugation. The transmitter can be released from this storage form by treatment with acid or a solution of sodium lauryl sulphonate or by heating.

It is suggested that the physiological nerve transmitter release mechanism involves a change of the state of the storage units allowing the contents to diffuse out.

Euler, U. S. v., Pharmacol. Rev. 1954. 6. 15.
Euler, U. S. v., Second Internat. Neurochem. Symposium, Aarhus 1956. In press.
Euler, U. S. v. and N.-Å. Hillarp. Nature, London. 1956. 177. 44.

***Fernö, O. and B. Högberg** (AB Leo, Helsingborg, Sweden): HOW TO PROLONG THE EFFECT OF DRUGS.

An advantage of giving drugs in a form where a prolonged effect is obtained is that the drug can be administered with longer intervals. Another advantage may be that a more constant blood concentration is obtained, while in ordinary medication a curve representing the blood concentration as a function of time shows, as a rule, great fluctuations. The peaks then represent increased risks of side-effects and the dips intervals where the drug in question may have no therapeutic effect at all.

Starting with the combination of insulin and protamine, a survey is given on the various methods hitherto applied.

The methods may be divided into:

1. Delayed absorption (commonest method).
2. Delayed chemical inactivation (SKF 525A: ACTH-polyphloretin phosphate).
3. Delayed excretion (penicillin-probenecid).
4. Inactive compound metabolized to active drug (polyestradiol phosphate).

The authors conclude that the question of searching for new methods of producing long-acting drugs is to be regarded as very important.

* Paper read at the pharmacological meeting August 30th.

Fernö, O., B. Högberg and B. Uvnäs (Department of Pharmacology, Karolinska Institutet, Stockholm, and AB Leo, Helsingborg, Sweden): THE MECHANISM OF HISTAMINE RELEASE, II. (*cf.* Högberg, B. and B. Uvnäs).

Various theories have been proposed in order to explain the release of histamine in anaphylactic reactions, the action of histamine releasers etc. Enzymatic theories presuppose that histamine is anchored in the cell in firm chemical linkages which require enzymatic activity for their breakdown and the release of active histamine. As histamine releasing enzymes have been proposed proteases such as trypsin, fibrinolysin, etc. Other authors assume that histamine occurs in the tissues loosely anchored in chemical compounds which are easily broken up by changes in the physicochemical milieu.

It has become evident that the releasable histamine — at least in several animal species — is situated in the intracellular granules of the mast cells. Since the histamine can be rather easily obtained from the intracellular granules by mechanical and unspecific chemical treatment it seems likely that histamine is loosely anchored in the mast cells and not firmly bound there to some other compounds. »Disruption» of the mast cell membrane or leakage through it should then possibly lead to such physical disturbances inside the cell that the histamine should become free and appear outside the cell.

We have made some observations which support the idea that histamine liberation — at least under certain conditions — might be the result of an enzymatic »breakdown» of the mast cell membrane and the consequent leakage of histamine from its loose intragranular anchorage. Such a theory should satisfy both the advocates of an enzymatic mechanism and those of a physicochemical mechanism of histamine release.

Our observations are as follows. Histamine liberating fractions have been extracted from the eelworm from swine (Ascaris lumbricoides) and the stinging jellyfish (Cyanea capillata). The histamine liberator 48/80 as well as the releasers isolated from ascaris (asc) and from cyanea (cya) »disrupt» mast cells (from rat mesentery) and release histamine (from the

perfused cat's paw). A polysaccharide fraction prepared from hip seeds blocks both the actions of the three liberators. It also blocks the release of histamine occurring when antigen is added *in vitro* to sensitized guinea-pig tissue.

Assuming that the blocking action of the polysaccharide fraction was the result of an inhibition of an enzymatic mechanism we made the following experiments. Mast cells were incubated with 48/80 at 37° C. The influence on the action of 48/80 of various metal ions and other enzyme inhibitors, of temperature and of phosphorylating and dephosphorylating agents was observed. Of numerous enzymes investigated, among them trypsin, hyaluronidase, fibrinolysin and lipase, only phospholipases prepared from bee and snake venoms were found to be able to »disrupt» mast cells. The influence of metal ions and other enzyme inhibitors, temperature and phosphorylating agents on the »disrupting» action of phospholipases on mast cells was also investigated.

Our observations about the »fragmentary» action of 48/80 on the mast cell membrane might be valid not only for the mechanism of histamine release but also for the release of other biologically active substances occurring in the mast cell. They are also of interest for the discussions about the mechanism by which the release of active substances occurs from cells and bloodborne corpuscular elements.

Frankenhaeuser, B. and A. Persson (Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden): VOLTAGE CLAMP EXPERIMENTS ON THE MYELINATED NERVE FIBRE.

A voltage clamp technique for the myelinated nerve fibre has been developed in the following way: Changes in membrane potential were recorded at one node of Ranvier in an isolated nerve fibre with a technique (previously described, FRANKENHAEUSER 1957) in which the longitudinal current at

a petroleum jelly seal at one internode was led to the input of an amplifier while the output was fed back across another seal at the same internode. Changes in membrane potential then appear with negligible attenuation at the output of this feedback amplifier. This output signal was then led to the input of another amplifier. The output from this second amplifier was fed back across a seal at the neighbouring internode, located so that the node under investigation was between this seal and the earlier mentioned seals. The first system, with negative series feedback, provides in effect a high impedance recording instrument, whereas the second system, with negative parallel feedback, in effect stabilizes the potential across the nodal membrane. This potential was changed in desired steps with the aid of rectangular pulses biasing the second feedback amplifier, and the membrane currents associated with step depolarizations were recorded. These currents showed striking similarities with the squid fibre voltage clamp membrane currents (*cf.* HODGKIN *et al.* 1952 *a*, *b*, *c*, *d*). The currents were continuously graded with the voltage step. At moderate depolarizations an initial transient flow of inward current was followed by a lasting outward current. The initial current was outward at large cathodal polarizations. Reducing the external sodium concentration was associated with a distinct decrease of the initial inward current, and the voltage level at which the initial current reversed from inward to outward was shifted towards the resting potential level. The late outward current was largely unaffected by the external sodium concentration. An anodal polarization preceding the step depolarization was associated with an increase of the initial current, while a cathodal polarization was associated with a decrease. The quantitative analysis has yet to be carried out.

Frankenhaeuser, B., J. Physiol. 1957. *135*. 550.
Hodgkin, A. L., A. F. Huxley and B. Katz, J. Physiol. 1952 *a*. *116*. 424.
Hodgkin, A. L. and A. F. Huxley, J. Physiol. 1952 *b*. *116*. 449.
Hodgkin, A. L. and A. F. Huxley, J. Physiol. 1952 *c*. *116*. 473.
Hodgkin, A. L. and A. F. Huxley, J. Physiol. 1952 *d*. *116*. 497.

Fredriksson, T. (Research Institute of National Defence, Dep. I, Sundbyberg, Sweden): PHARMACOLOGICAL PROPERTIES OF FLUORO-PHOSPHORYLCHOLINES.

Methyl-fluoro-phosphorylcholine, its carbocholine analogue, its homocholine analogue and methyl-fluoro-phosphoryl-β-methylcholine, synthetized by TAMMELIN who has also shown that the compounds are powerful cholinesterase inhibitors, have been investigated. The compounds are extremely toxic, but their indirect cholinergic effects are to a certain extent reversible. They also have direct effects on cholinergic »receptors», and in this respect they show similar differences as acetylcholine, carbocholine, homocholine and acetyl-β-methylcholine. Those of the compounds which contain a quarternary nitrogen atom have no effects on the central nervous system. Preliminary results obtained with some organophosphorus thiocholines will also be discussed.

Tammelin, L.-E., Acta Chem. Scand., in press.

Fries, B. (Department of Pharmacology, Veterinärhögskolan, Stockholm, Sweden): INFLUENCE OF POLYPHLORETIN PHOSPHATE ON INCREASED CAPILLARY PERMEABILITY.

Polyphloretin phosphate belongs to a group of polymer high molecular weight compounds synthesized during recent years at the Research Laboratory of AB Leo. Polyphloretin phosphate (PPP) is a very strong inhibitor of hyaluronidase *in vitro*. *In vivo* it has been shown to have an antihyaluronidase effect too, *viz.* by reducing the permeability of the peritoneum when employed locally. This permeability reducing effect has been used to prevent experimentally provoked intraperitoneal adhesions. A general effect in the body after administration of PPP has hitherto not been found.

In the present work a study has been made to ascertain whether any general effect of PPP could be obtained after

intravenous injection. The first aim has been to investigate if experimentally induced oedema in the legs of white rats could be prevented by PPP.

Ovalbumin has been used in the same manner as by HALPERN and BRIOT (1950), *viz.* intraperitoneally, to produce a capillary damage with subsequent oedema. Simultaneously with the injection of ovalbumin, intravenous injection of Evans Blue has been done in order to visualize the oedema. One hour after injection of ovalbumin the feet of the rat will have a pronounced oedema, the skin being strongly blue-coloured by Evans Blue staining the plasma. Another group of rats has got PPP intravenously ½ hour before injection of ovalbumin. The results of these experiments are recorded and discussed.

Halpern, B. N. and M. Briot: Arch. Int. Pharmacodyn. et Thérapie 1950. 82. 247.

Gemzell, C. A., H. Robbe and G. Ström (Karolinska Sjukhuset, Department of Obstetrics and Gynecology and Department of Clinical Physiology, Stockholm, Sweden): ON THE DISTRIBUTION OF CARBON MONOXIDE BETWEEN HUMAN MATERNAL AND FETAL BLOOD IN VIVO.

A given amount (20—30 ml) of carbon monoxide was administered via a closed respiratory system to healthy women in labour at different times before delivery, and the carboxyhemoglobin concentration repeatedly measured. After the carbon monoxide exposure, the women either breathed oxygen in a closed system up to delivery (short periods), or room air freely (long periods). The carboxyhemoglobin and oxyhemoglobin concentrations in the umbilical vein (fetal blood) immediately after delivery were compared to the simultaneous carboxyhemoglobin concentration in maternal blood.

Half an hour after exposure, the fetal carboxyhemoglobin concentration had risen to less than half the maternal concentration. Identical fetal and maternal concentrations were not attained until after several hours. Still later the fetal concentration rose well above the maternal one.

Fetal blood thus eventually acquires a higher carboxyhemoglobin concentration than maternal blood, as theoretically expected, but the carbon monoxide transport from maternal to fetal circulation is slow.

Giacobini, E. (Department of Physiology, Karolinska Institutet, Stockholm, Sweden): THE INTRACELLULAR DISTRIBUTION OF CHOLINESTERASE IN THE NERVE CELL STUDIED BY MEANS OF A QUANTITATIVE MICROMETHOD.

In a series of investigations, the distribution of ChE (cholinesterase) and AChE (acetylcholinesterase) has been studied, by means of a microgasometric technique using the cartesian diver (GIACOBINI and ZAJICEK 1956) and a histochemical thiocholine method (GIACOBINI 1956) in single neurones belonging to sympathetic (GIACOBINI 1957) and spinal ganglions (GIACOBINI a) and to the anterior horn (GIACOBINI and HOLMSTEDT) of the spinal cord of rat. The ChE activity has also been determined, by means of a more sensitive diver technique (GIACOBINI b), in $\mu\mu$l samples of cyto- and nucleoplasm, in single nucleoli and in small segments of dendrites and axons of anterior horn cells of rat. A sample of 0.01 $\mu\mu$l cytoplasm was found to exhibit a ChE activity of about 4.8×10^{-6} μl CO_2/hour corresponding to the hydrolysis of about 625 pg (1 pg=10^{-12} g) acetylthiocholine, and a sample of 0.01 $\mu\mu$l nucleoplasm showed a ChE activity of 0.41×10^{-6} μl CO_2/hour corresponding to the hydrolysis of about 55 pg acetylthiocholine.

The results of these investigations, together with those obtained by previous histochemical and biochemical work, demonstrated with the help of a selective inhibitor (Mipafox) that AChE is present in some of the cells of sympathetic and spinal ganglions and in all the anterior horn cells.

The results demonstrated also that AChE is highly concentrated in the neurones and their processes and that the enzyme is not strictly localized to a part of the cell but is

present in different concentrations in the different parts. The cellbody exhibits higher values of AChE activity, the axon and the dendrites a somewhat lower one and the nucleus has an activity 10—100 times lower than the other parts; the nucleolus does not show any measurable activity.

Finally, a difference was found in the intracellular distribution of the enzyme in cells of different origin, namely, the distribution pattern found in the cellbody and in the axon of the anterior horn cells differs from that found in the spinal ganglion cells, and the enzyme was found to be present in higher concentration in the sympathetic and anterior horn cells than in the spinal ganglion cells. A functional significance of such a peculiar distribution of the enzyme is suggested.

Giacobini, E., Acta Physiol. Scand. 1956. *36*. 276.
Giacobini, E. and J. Zajicek, Nature, London 1956. *177*. 185.
Giacobini, E., J. Neurochem. 1957. *1*. 234.
Giacobini, E., Acta Physiol. Scand. a, in press.
Giacobini, E., Exptl. Cell Research b, in press.
Giacobini, E. and B. Holmstedt, Acta Physiol. Scand., in press.

Graf, K. and S. Rosell (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): CONTINUOUS RECORDING OF MUSCLE BLOOD FLOW IN CATS WITH A HEATED THERMOCOUPLE.

The blood flow in the right gastrocnemius muscle of anesthetized cats was determined, using the thermal method described by HENSEL *et al.* (1954). The blood from the femoral vein on the contralateral side was allowed to pass a photoelectric drop counter operating an ordinate recorder.

Changes in blood flow were produced by intraarterial injections of adrenaline or acetylcholine or by electric stimulation of vasodilator pathways within the hypothalamus.

In order to determine the exact position of the thermocouple needle the muscle was dissected after the experiment.

The dissection of the muscles showed that in those experiments where the thermocouple failed to record changes in

blood flow, the distance between the needle and *visible* vessels was 4—5 mm or more. If the needle was closer to a *visible* vessel, the thermocouple was able to record changes in blood flow.

These findings suggest that the heated thermocouple, modified by HENSEL *et al.*, records blood flow in large vessels rather than the capillary blood flow in muscle.

A comparison between the two methods used for measuring blood flow shows quite a good agreement in the recordings, both quantitatively and in time course, in those cases where the needle was properly placed.

Hensel, H., J. Ruef and H. Golenhofen, Pflügers Arch. ges. Physiol. 1954. 259. 267.

Graf, W. (S:t Eriks Hospital, IInd Medical Service, Stockholm, Sweden): THE EFFECT OF PITRESSIN AND HISTAMINE ON HUMAN SKIN AND DEEP TEMPERATURES.

Thermocouples have been used to measure skin, rectal, gastric and liver temperatures with five minute intervals. If pitressin is given, a drop of the skin temperature ensues, but a rise of the temperatures of inner organs. These, however, do not behave identically: the temperature of the stomach displays a greater rise than the rectal and liver temperatures. Histamine elicits a rise of skin temperature but lowers the temperatures of inner organs. If pitressin is administered before histamine, the effect of the latter drug is notably reduced, whereas histamine does not appear to suppress the effect of pitressin. Certain seasonal differences seem to exist in the behaviour of the temperatures.

Grant, R., P. Lindgren, A. Rosén and B. Uvnäs (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): THE RELEASE OF CATECHOLS FROM THE ADRENAL MEDULLA ON ACTIVATION OF THE SYMPATHETIC VASODILATOR NERVES TO THE

SKELETAL MUSCLES IN CATS BY HYPOTHALAMIC AND MEDULLARY STIMULATION.

Sympathetic vasodilator nerves to the skeletal muscles in the cat were activated by topical electric stimulation in hypothalamus and medulla oblongata. Histological examinations of the brains were performed. The blood flow from a skinned hindlimb was recorded in the femoral vein. Blood from the left adrenal was collected in a cold milieu and immediately centrifuged. The adrenaline and noradrenaline fractions were separated chromatographically, mainly following the procedure described by VOGT 1952. The amounts of adrenaline and noradrenaline were determined by biologic assay using the cat's uterus and colon. The spontaneous secretion varied considerably; for adrenaline between 0.010 and 0.100 μg per kilogram per minute and for noradrenaline between 0.060 and 0.600 μg per kilogram per minute. During stimulation of the sympathetic vasodilator pathway in hypothalamus we found a marked increase of the adrenaline fraction in the adrenal vein, from 75 % up to 1 500 % and in a few cases even more. The increase of noradrenaline was moderate, from 25 % up to 200 % and in two cases somewhat more.

When the vasodilator pathway was stimulated in the medulla oblongata we did not find the same relationship between adrenaline and noradrenaline output; the amount of adrenaline varied from 150 % up to 500 % and noradrenaline from 50 % up to 250 %. The results will be discussed.

Vogt, M., Brit. J. Pharmacol. 1952. 7. 325.

Gräsbeck, R., W. Nyberg, G. Perman and P. Reizenstein (Serafimerlasarettet, Department of Medicine, Stockholm, Sweden, and Medical Clinic IV, Maria Hospital, University of Helsinki, Finland): EXCRETION OF ENDOGENOUS VITAMIN B_{12}.

The present study was performed in an attempt to elucidate the following questions:

1. How fast can the body pool of vitamin B_{12} be exhausted when no absorption takes place?

2. Does any breakdown of B_{12} occur in the body, or is the amount excreted equal to that absorbed?

3. Which is the minimum amount of B_{12} which must be replaced by absorption or parenteral administration per day?

The excretion of vitamin B_{12} after parenteral administration of 0.5 μg $B_{12}Co^{56}$ has been studied in humans. The fecal excretion was followed for four weeks in five normal volunteers and was found to be 1.5 ± 0.1 mμg $B_{12}Co^{56}$ per day. The excretion of endogenous vitamin B_{12} was estimated to be 5.8 μg per day. This figure was based on the assumption that the vitamin administered was evenly distributed in the body pool of vitamin B_{12} (assumed to be 2 mg). The biliary excretion was studied in six patients with postoperative drainage of the common bile duct during four to ten days after administration of the labelled vitamin. It was found to be 4.6 ± 1.0 mμg of $B_{12}Co^{56}$, corresponding to 16.8 μg of endogenous B_{12} per day.

Since it is not possible to collect bile quantitatively, the $B_{12}Co^{56}$-concentration in bile was related to the bilirubin concentration and the total daily excretion was calculated, assuming a total bilirubin excretion of 270 mg. The $B_{12}Co^{56}$-excretion values of the first three days were disregarded because of evident flushing effects.

These preliminary data indicate that in the intestine as much as about 75 per cent of the biliary vitamin B_{12} are reabsorbed. On the basis of the fecal excretion values observed the time required for a normal person to develop pernicious anemia after total gastrectomy could be calculated to be two to three years. This is close to the time required, as observed clinically, in postgastrectomy patients.

The calculated daily loss of B_{12} was at least not smaller than the amount which can be presumed to be absorbed from the food per day, and it is larger than the minimum maintenance dose of pernicious anemia patients. There are thus no indications that a breakdown of vitamin B_{12} takes place.

Gribbe, P.-O., L. Hirvonen and J. Lind (Wenner-Gren Research Laboratory, Norrtulls sjukhus, Stockholm, Sweden, and Institute of Physiology, University of Turku, Finland): THE DYNAMICS OF THE LEFT HEART STUDIED BY CINE-ANGIOCARDIOGRAPHY WITH SIMULTANEOUS ECG-RECORDING.

Angiocardiography has been performed on dogs using cineradiography at 50 pictures per second. The electrocardiogram has been recorded synchronously with each exposure.

The films have been studied in a projector as endless loops, picture by picture. This high speed cineradiography has made it possible to analyze the different phases of the cardiac cycle, including changes in shape and size of the opacified heart cavities.

The cyclic changes in size of the left atrium and the left ventricle have been determined in the right oblique projection. Due to the symmetric rounded form of both these heart cavities their capacity can be calculated by geometry.

The volumes obtained from the series of pictures have been plotted against the simultaneously recorded ECG. The residual blood in the left ventricle has been calculated as well as the stroke volume of the left ventricle. Good agreement has been obtained with simultaneously determined cardiac output according to FICK.

Guld, C. (Institute of Neurophysiology, University of Copenhagen, Denmark): METHOD OF VACUUM TUBE SELECTION FOR DIRECT-COUPLED AMPLIFIERS.

Direct-coupled amplifiers in electrophysiology require properties of vacuum tubes which are not specified by the manufacturers. These properties vary considerably in tubes of the same type. In the following a method is described for the systematic testing of one of these properties: Direct-current changes in the vacuum tube characteristic as a function of

time (D. C. drift). To this purpose an attempt was made to exclude all external factors influencing the tube characteristic.

The tube was circuited as cathode follower, the tube itself being the one arm of a bridge circuit; the cathode resistor R_c and two fixed resistors R_a and R_b were the other three arms of the bridge. With the bridge in balance the voltage across R_a equalled the plate cathode voltage E_b, and the voltage across R_c (and R_b) determined the plate current I_b. A tap on R_b provided the grid voltage E_g. To balance the bridge, E_g was varied in such a way that the voltage e_d between the output terminals of the bridge was adjusted to zero. Due to the negative feedback of the cathode follower, e_d was nearly equal to the changes in E_g at constant I_b and E_b. This circuit has the advantage that e_d is insensitive to variations in the supplying voltage E_{bb}, the vacuum tube acting in its bridge arm as a linear element of constant resistance.

The bridge output e_d was recorded on a multiple point recorder via a floating chopper-stabilized direct-coupled amplifier. The amplifier and the recorder were insulated from currents to ground by means of a doubly screened power transformer.

I have especially investigated the vacuum tube EF 804 (Telefunken). The D. C. drift e_d caused by a variation in external conditions was:

1. 10 mV per mA variation in filament current (S. D. = 1.0, time constant less than 0.5 min).
2. 0.6 mV per °C variation in external air temperature (S. D. = 0.12, time constant about 5 min).
3. 2 mV per V variation in supplying voltage E_{bb}.

On the basis of these data the external conditions were stabilized, the drift resulting from them being less than 50 μV per hour. This allowed a measurement of e_d originating from changes in the internal tube properties. The tubes were aged at the operating point for 250 hours without interruption, allowed to cool and measured for D. C. drift over a four hour period.

The variability in vacuum tube properties is illustrated by the finding of 62 per cent of tubes with a drift at the end

of the four hour period of less than 0.5 mV per hour in one batch (100 tubes) as compared with 10 per cent in another batch. Correspondingly in the former batch there was no tube with a drift exceeding 4 mV per hour as compared with 27 per cent in the latter.

The D. C. drift resulting from a change in the voltage between cathode and filament from zero to 125 V averaged 0.2 mV (0 to 1 mV) with $R_c = 30$ KΩ. With $R_c = 600$ KΩ the D. C. drift was still lower.

Haaranen, A., M. Hintsanen, E. Jalavisto, E. Kauhanen and A. Nederström (Institute of Physiology, University of Helsinki, Finland): THE EFFECT OF INHALATION OF ALCOHOL AND ETHER ON THE MECHANICS OF BREATHING.

The surface tension at the air-fluid interface of the lung alveoli has been claimed to constitute one of the major factors in the elastic recoil of the lungs (v. NEERGAARD 1929). This hypothesis is based on experiments with isolated lungs. The aim of the present paper is to investigate whether it is possible to affect *in vivo* the mechanics of breathing and particularly the lung elastance by inhalation of volatile agents that have a smaller surface tension than water.

As experimental animals atropinized and anaesthetized cats and rabbits were used. The pleural pressure was registered either with a rubber membrane manometer on smoked drum or in later experiments optically on photographic film. The respiration was recorded with a Marey's tambour, the animal being in a body plethysmograph, or in later experiments optically with a Fleisch pneumotachograph. In the former experiments the expiratory inspiratory pleural pressure differences, Δp dyn., were compared with the difference in volume, ΔV, and in the later experiments the static pleural pressure difference, Δp stat., with the volume difference, ΔV stat., likewise at zero flow.

Both the $\frac{\Delta p}{\Delta V}$ dyn. and $\frac{\Delta p}{\Delta V}$ stat. were shown to decrease after inhalation of ether and to a lesser degree after inhalation of alcohol; the effect was, however, often masked by variations in bronchiolar tone occurring in spite of atropinization.

Neergaard, K. von, Ztschr. exper. Med. 1929. *66.* 373.

Hagbarth, K. E. and E. Kugelberg (Serafimerlasarettet, Department of Neurology, Stockholm, Sweden): SPINAL MECHANISM AND INTEGRATION OF HUMAN ABDOMINAL AND ERECTOR TRUNCI SKIN REFLEXES.

It has long been a matter of dispute whether the human abdominal skin reflex is mediated by a long cerebral arc or whether it is a strictly spinal reflex. In the present study the reflex has been analyzed by electromyographic technique. The investigation has shown that it is a spinal polysynaptic reflex, which often has an extensive irradiation and a wide range of latency. The response with the shortest latency, however, is found in a relatively small portion of the abdominal muscles in the vicinity of the stimulated skin area where the contraction is most vigorous.

The abdominal reflex is not based on a simple segmental organisation which is shown by the fact that stimulation of various regions within the same dermatome may give rise to widely different reflex patterns. An abdominal skin stimulus near the midline will not only cause a bilateral contraction of the abdominal muscles but also a bilateral reciprocal inhibition of the trunk erector muscles. This tends to bend the trunk forward. A stimulus near the dorsal midline of the trunk within the same dermatome may, on the other hand, cause a contraction of the erector muscles and a bilateral reciprocal abdominal inhibition. This tends to bend the trunk backwards. Finally, intermediate stimuli will give rise to bilateral patterns of contraction and inhibition in the muscles of abdomen and dorsum so that the trunk tends to bend towards the side in the direction of the stimulus.

It appears that the abdominal as well as the erector trunci skin reflexes represent an elaborate spinal defense mechanism in which each skin area of the trunk is functionally connected with the appropriate withdrawal and protection muscles. At whichever point on the circumference of the trunk the nociceptive stimulus is applied it results in a movement away from the stimulus as well as a contraction of adjacent muscles for protection of the underlying tissues.

Hagbarth, K. E. and E. Kugelberg (Serafimerlasarettet, Department of Neurology, Stockholm, Sweden): PLASTICITY OF THE ABDOMINAL SKIN REFLEX.

Our knowledge of spinal cord reflexes is based mainly on experiments on either anesthetized or on spinal or decerebrate animals. Relatively little is known about these reflexes in the intact organism. The human abdominal skin reflex is an example of a spinal polysynaptic reflex that can easily be analyzed in intact and unrestrained subjects and hence it offers an opportunity of studying how spinal mechanisms are integrated with the function of higher centers.

A striking feature of this reflex is the variability of the stimulus threshold and its intimate correlation to cerebral function. By repetition of a non-painful abdominal skin stimulus the threshold can be raised until the reflex is completely extinguished. This habituation is a cumulative process that can be built up to a considerable strength and duration. It is also a discriminating process since the maximal habituation always affects the particular stimulus that has been repeated. In this sense the habituation has specificity in regard to both the localization and the modality of the abdominal skin stimulus.

The results with painful stimuli are quite different. Repetition of such stimuli causes a lowering of the threshold and an increase in the strength and irradiation of the reflex. A long-lasting sensitization of the reflex can often be obtained by a single nociceptive abdominal skin stimulus. Since this process

is not strictly specific in regard to the localization of the stimulus it causes a widening of the receptive field. The most efficient way to evoke a sensitization is to apply a heavy abdominal blow in which the skin contact is automatically combined with a painful visceral stimulus that in itself causes a powerful contraction of the abdominal muscles. It is not clear to what extent the pairing of these two stimuli is of significance and if it can be maintained that the skin stimulus has been conditioned in the Pavlovian sense by the visceral stimulus. Preliminary differentiation experiments, however, seem to support this view.

The processes of habituation and sensitization are intimately correlated to the subject's state of expectancy. The effects may be totally lost if the subject is allowed to be aware of the quality of the approaching stimuli and often a marked sensitization of the reflex can be obtained simply by informing the subject that a painful abdominal stimulus may occur.

The results show that in the intact organism a spinal polysynaptic reflex can be modified and adapted in an appropriate way by a tonic cerebral outflow which has the capacity to regulate spinal internuncial relays. By the specificity of its action temporary spinal reflex patterns can be established, allowing appropriate responses with a minimal latency. It remains to be settled to what extent specificity of spinal cord reflexes is a result of integrative processes in higher centers.

Håkansson, C. H. (Institute of Neurophysiology, University of Copenhagen, Denmark): ACTION POTENTIALS AND MECHANICAL RESPONSE OF ISOLATED FROG MUSCLE FIBRES.

Simultaneous recording of the intracellular and extracellular action potentials and of the twitch tension of the single cross striated muscle fibre showed that the extracellular action potential coincided with the rising phase of the intracellularly recorded action potential. The extracellularly recorded action potential terminated in the middle of the mechanical latency

(20° C) when correcting for the time required for the potential to propagate to the recording electrode.

The rectilinear relationship between conduction velocity and fibre diameter (HÅKANSSON 1956) has been interpreted as being due to different membrane characteristics for fibres of different diameter. This assumption is supported by the effect of stretch on conduction velocity. Up to a stretch of 50 per cent of equilibrium length the velocity for all fibres remained constant. Above 50 per cent of stretch the velocity increased, exceeding the velocity at equilibrium length by 15 to 50 per cent at 100 per cent of stretch. The highest value was recorded from the fibres with the largest diameters.

The changes in the conduction velocity and the amplitude of the extracellularly recorded action potential were, however, small as compared with the large decrease in twitch tension with increasing stretch. At 100 per cent of stretch the action potential amplitude was reduced by 40 per cent, while twitch tension could no longer be discriminated. This effect was reversible. The change in amplitude can be accounted for in terms of the different current distribution which arises from the decrease in fibre diameter with stretch.

With the fibre surrounded by a thin layer of Ringer's solution (impedance 12 megohms per cm), the conduction velocity was reduced to half its value in Ringer's solution. The twitch tension was only reduced by 20 per cent. The decrease in conduction velocity was accompanied by a 50 per cent increase in mechanical latency.

Håkansson, C. H., Acta Physiol. Scand. 1956. 37. 14.

Halme, A. A., K. J. W. Hartiala and O. J. Kassila (Institute of Physiology, University of Turku, Finland): EFFECT OF ETHIONINE ON THE GLUCOSE AND STARCH TOLERANCE TESTS.

Ethionine, the ethyl analogue and antimetabolite of methionine, was given to rabbits, resulting in the usual production

of pancreatitis with accompanying moderate fatty metamorphosis of the liver. As in numerous previous studies the endocrine pancreas showed no significant histological changes.

Glucose and starch tolerance tests were performed on rabbits before and after the ethionine treatment. The results were treated in the following manner: the maximal rise in blood sugar during the glucose and the starch tolerance tests was determined by subtracting the value for the fasting blood sugar of each curve from that of the peak of the respective curves. Then, the extent to which the maximal rise in blood sugar after glucose exceeds that after starch was calculated in percentages of the maximal rise after starch. The »test per cent» calculated by this means revealed a significant rise after ethionine treatment. The mean »test per cent» during the control period was 32, standard deviation being 19. The normal range calculated from these figures lies between —6 and +70. The mean results after 4—6 days' treatment with ethionine was 239, after 9—11 days it was 546.

The mean slope of the glucose tolerance curves remained unchanged during the first half hour before and after ethionine treatment. This suggests an undisturbed absorption of glucose. The continued rise in the glucose tolerance curve with a marked lowering of the starch tolerance curve was a characteristic feature for the period of ethionine treatment. In addition, the initial values for the fasting blood sugar showed a slight elevation during the administration of ethionine. These findings are taken as an indication that in addition to the lowering of the amylolytic activity of the pancreas an insufficiency of the endocrine function of the pancreas is present.

CASTRINI (1954) has reported an interesting histochemical study of the presence of ethionine-induced changes also in the endocrine pancreas with the correlative changes in the liver. Our results are in some respects in accordance with this study. In other respects, our results are similar to those reported by ALTHAUSEN and UYEYAMA (1954) in patients suffering from chronic pancreatitis. They also lend support to their claim

of the suitability of this test for studies of the exocrine function of the pancreas.

Althausen, T. L. and K. Uyeyama, Ann. Int. Med. 1954. *41*. 563.
Castrini, G., Riv. di Biol. 1954. *46*. 481.

Halme, A. A., K. J. W. Hartiala and K. A. Pekanmäki (Institute of Physiology, University of Turku, Finland): EFFECT OF CORTISONE ACETATE ON THE GLUCURONIDE DETOXICATION SYNTHESIS OF THE LIVER AND DUODENUM IN RATS.

Numerous studies have been reported as to the effect of cortisone on the gastrointestinal tract, especially on the gastric secretion. Recently HARTIALA (1955) has shown that contrary to previous concepts glucuronide synthesis is carried out to a marked extent also in the mucous membrane of the alimentary canal. The purpose of the present investigation was to study the effect of cortisone acetate on the glucuronide synthesis of the liver and duodenum.

Altogether 46 male albino rats were used in this study. This material was divided into two groups as follows. Group 1 comprised 25 rats. Fourteen of them received daily doses of 12.5 mg cortisone acetate intramuscularly over a period of 6—10 days before the test. Eleven untreated rats were used as controls. Group II comprised 21 rats. Twelve of them received daily doses of 25 mg cortisone acetate over a period of 10 days. Nine untreated animals served as controls.

The detoxication synthesis was followed by using o-aminophenol as a substrate and measuring the glucuronide formed with it. The procedure has been described previously (LEVVY and STOREY 1949, HARTIALA and RONTU 1955). The results are expressed as γ of o-aminophenol conjugated per 100 mg dry weight of tissue.

No marked changes were found in the glucuronide synthesis of the liver after the administration of cortisone acetate.

Duodenum tissue slices gave the following mean ranges. Group I: controls 217 $\pm$ 11.0, cortisone treated rats 150 $\pm$ 9.2,

mean difference 67 ± 14.3. Group II: controls 237 ± 23.9, cortisone treated rats 135 ± 5.4, mean difference 102 ± 24.5.

Preliminary experiments have also been carried out using cortisone acetate as a substrate in presence of o-aminophenol. The results seem to indicate that cortisone acetate also has a depressive effect *in vitro* on the glucuronide synthesis of the duodenal mucosa.

Hartiala, K. J. W., Ann. Med. Exper. Fenn. 1955. *33*. 239.
Hartiala, K. J. W. and S. Rontu, Ann. Med. Exper. Fenn. 1955. *33*. 213.
Levvy, G. A. and I. D. E. Storey, Biochem. J. 1949. *44*. 295.

Hammel, H. T., K. Lange Andersen, Y. Løjning and P. F. Scholander (Physiology Department, University of Pennsylvania, USA, Institute of Aviation Medicine, Royal Norwegian Air Force, and Navy Medical Office, Oslo, and Institute of Zoophysiology, University of Oslo, Norway):
METABOLIC ACCLIMATION TO COLD IN MAN.

In September and October eight men lived out in the Norwegian mountains above tree line in essentially summer clothing and with insufficient night protection. Snow and sleet were common, and night temperatures were usually between 0 and +5° C. The men had enough food, and kept busy hiking, fishing and hunting. The nights were spent underneath a tarpaulin rigged as a rainproof shelter with one side open. The subjects slept, naked except for socks and shorts, in a single blanket sleeping bag with a hydrophobic cover. After six weeks in the field they had acquired a considerable acclimation. Tests showed that they then stayed warm from head to foot all night, and slept well. Heat production remained 50—60 % higher than the basal all night, and while they were asleep. Shivering, visible or detectable by electromyography, occurred frequently during sleep. Control subjects had a less elevated metabolic rate and were unable to rest and sleep due to chilling, especially of the feet. In the acclimated men, therefore, an increased heat production alleviated the shell cooling from which unacclimated people suffer. When bicycling naked in the cold, just enough

to maintain the rectal temperature, the cold-acclimated men used as much oxygen as the controls, so neither during exercise nor during rest did acclimation result in increased insulation by shell cooling. Metabolic acclimation to cold is well known in other homeotherms.

*Hanngren, Å. (Department of Pharmacology, Veterinärhögskolan and Söderby Sjukhus, Stockholm, Sweden):
AUTORADIOGRAPHICAL STUDIES OF THE DISTRIBUTION OF P-AMINO-SALISYLIC ACID (PAS) IN THE BODY.

A brief description is given of the methods of labelling p-amino-salisylic acid with C^{14} and H^3. C^{14}-labelled NaPAS was made with a radiochemical synthesis and H^3-labelled PAS with recoil tritons in a reactor. Chromatographical methods were used in the control of the purity of the substances. The studies of the distribution in the body were partly carried out in mice. Full-section autoradiograms were made according to the method of ULLBERG (1954). Experiments in rabbits gave a final dilution-volume in 15 minutes and the distribution-volume was less than the extracellular space. The autoradiograms also show a higher PAS-content in the blood and excretory organs than in other tissues with a few exceptions. The excretion was very rapid via the kidneys and the intestinal juice. As early as 5 minutes after an intravenous injection the intestinal tract showed PAS-content. The gallbladder, however, was empty. After 30 minutes the blood and tissue content of PAS was decreasing and after 2 hours only the intestines showed PAS-content. Detailed autoradiographic studies show, *e. g.*, inability of PAS to penetrate the blood-cerebrospinal fluid barrier in non-infected animals. A high concentration in the skin and in the sclera and lens of the eye could also be observed. Autoradiograms of C^{14}-NaPAS and H^3-PAS were identical.

Ullberg, S., Acta Radiol. Stockh. 1954. Suppl. 118.

* Paper read at the pharmacological meeting August 30th.

Hansson, C-H. (Department of Surgery, Veterinärhögskolan, Stockholm, Sweden): BIOCHEMICAL AND PHARMACOLOGICAL STUDIES WITH SUCCINYLCHOLINE IN DOMESTIC ANIMALS.

The hydrolysis of succinylcholine in the blood of different domestic animals has been studied with the aid of an electrometrical method. There was no relationship between succinylcholine esterase activity and the activities of other esterases measured with the following substrates: acetylcholine iodide, acetyl-β-methylcholine iodide and butyrylcholine iodide. Furthermore, there was no positive correlation between esterase activity and the dose response *in vivo* to succinylcholine. However, animals with measurable succinylcholine esterase activity had greater tolerance to the drug than other animals. The dose suitable for different surgical interventions was determined with the aid of nerve-muscle preparations.

The effects of succinylcholine on respiration and blood pressure will be discussed.

Hansson, E. (Department of Pharmacology, Veterinärhögskolan, Stockholm, Sweden): STUDIES ON THE INCORPORATION OF S^{35}-METHIONINE IN THE PANCREAS AND THE ENZYMES OF PANCREATIC JUICE.

By autoradiographical studies using whole mice sections it has been observed that the mouse pancreas shows higher uptake of intravenously injected S^{35}-methionine than any other organs and tissues in the body. This observation has also been confirmed by separate radioactivity measurements. Autoradiograms were also made by the strippingfilm technique on histological sections of the pancreas and thus the localization of the radioactivity can be done at a cellular level. The radioactivity is concentrated in acini and ducts after about one hour.

The rate of appearance of radioactivity in the pancreatic juice after an intravenous application of S^{35}-methionine has been studied on anesthetized cats. A polyethylene cannula was introduced into the main pancreatic duct just above its entrance into the duodenum. By continuous intravenous injection of pancreozymin and secretin a continuous flow of pancreatic juice has been obtained. The juice has kept a fairly constant enzyme and protein content during the 6—8 hours covered by the experiments.

G-M measurements showed that an appreciable radioactivity appeared in the pancreatic juice 50—60 minutes after the injection. 2—3 hours later there was a considerable decrease in the activity. By paper electroforesis of the pancreatic juice four of five fractions holding most of the radioactivity can be separated. The enzymatic activity of these fractions has been estimated.

Harboe, M. and F. V. Lorentzen (Institute of Aviation Medicine, Royal Norwegian Air Force, Oslo, Norway): VENTILATORY STUDIES OF THE LUNGS DURING CONTINUOUS PRESSURE BREATHING (CPB).

The nitrogen clearance of the lungs during oxygen breathing has been investigated by means of the nitrogen meter during continuous pressure breathing compared with normal conditions. In all 135 experiments have been made on 5 healthy subjects. The degree of uneven ventilation, nitrogen wash-out time, nitrogen wash-out volume and lung clearance index have been investigated.

Increasing tidal volumes gave more even ventilation in some subjects but no change in others. The nitrogen clearance pattern remains stable with CPB and normal respiration. The changes in ventilation-perfusion relationship when switching to CPB can probably — when the ventilation does not undergo any important change — be attributed to changes in blood perfusion of the lungs during CPB.

Hartiala, K. J. W. (Institute of Physiology, University of Turku, Finland): STUDIES ON THE GLUCURONIDE SYNTHESIS BY THE GASTROINTESTINAL MUCOUS MEMBRANE AND ITS ROLE IN THE DETOXICATION AND ABSORPTION MECHANISMS.

Glucuronide conjugation belongs to the mechanism by which a large group of phenol and aromatic compounds and steroids are coupled in the organism and in which form they are also excreted in the urine.

Liver has been considered the main site of this detoxication function. By using o-aminophenol our previous studies have shown that also the mucous membrane of the gastrointestinal tract participates in this synthesis (HARTIALA 1954, 1955).

Further evidence of the intestinal glucuronide synthesis has been obtained. Feeding of cinchophen, known to be a glucuronogenic substance, results in a marked increase in the glucuronide content of the portal blood. This is evident also after the ligation of the common bile duct. Incubation of phenolphthalein with tissue slices from various organs shows that in the mucous membrane of the gastrointestinal tract there results also formation of phenolphthalein glucuronide. The nature of this conjugate has been studied using β-glucuronidase. This enzyme is capable of splitting the formed conjugate to free phenolphthalein. Saccharate, an inhibitor of this enzyme, also prevents the hydrolysis of the intestinal glucuronide conjugate.

Experimental evidence has been obtained which indicates that the hepatic and intestinal glucuronide syntheses do not behave similarly under various conditions. The hepatic glucuronide conjugation is increased by thyroxin treatment of the animals (HARTIALA, HIRVONEN and KASSINEN 1956). During hypothyreosis (by using radioactive I^{131}) the hepatic glucuronide synthesis capacity is depressed (HARTIALA and HIRVONEN 1956). In the same experiments the intestinal glucuronide synthesis was not changed from normal. Cortisone depresses the glucuronide synthesis *in vitro*.

From available information it seems likely that the

glucuronide formation and production of mucus are competitive functions of the mucous membrane. By using large amounts of glucuronogenic substances the detoxication mechanism is carried on at the cost of the mucous secretion (HARTIALA, IVY and GROSSMAN 1950). On the other hand some other intestinal functions, *e. g.* glucose absorption, is not impaired by simultaneous feeding of glucuronogenic substances. It appears that the selective absorption in the gastrointestinal tract involves separate enzyme systems for the absorption of carbohydrates and for the formation of glucuronides. The production of the latter compounds by the mucous membrane might be considered as another type of selective absorption system which changes insoluble substances into a soluble form and allows them to pass through the intestinal wall in this form. The final achievement of such changes might not always mean a protective detoxication measure for the organism against harmful chemical agents, since the list of glucuronogenic substances includes also a great number of agents known to be cancerogenic.

Hartiala, K. J. W., Acta Physiol. Scand. 1954. *31.* suppl. 114. 20.
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Hartiala, K. J. W. and L. Hirvonen, Ann. Med. Exp. Fenn. 1956. *34.* 122.
Hartiala, K. J. W., L. Hirvonen and A. Kassinen, Ann. Med. Exp. Fenn. 1956. *34.* 117.
Hartiala, K. J. W., A. C. Ivy and M. I. Grossman, Am. J. Physiol. 1950. *162.* 110.

Hauberg Johansen, S. and W. Hougs (The Research Laboratory of GEA, Ltd., Copenhagen, and the Anaesthesia Laboratory, Copenhagen County Hospital, Gentofte, Denmark):

5-HYDROXYTRYPTAMINE AND NEUROMUSCULAR BLOCKING AGENTS.

On cats, anaesthetized with chloralose, the contractions of the indirectly stimulated anterior tibial muscle and the soleus muscle were recorded kymographically during continuous intravenous infusion of the following neuromuscular blocking agents: d-tubocurarine chloride, benzoquinonium and decamethonium.

When a stable level of neuromuscular depression was reached, 5-hydroxytryptamine in doses of 30 to 300 μg/kg was injected intravenously.

Under these circumstances, 5-hydroxytryptamine displayed an antagonistic action to d-tubocurarine and benzoquinonium, whereas no such evident action could be demonstrated with decamethonium.

Hirsjärvi, E. (Institute of Physiology, University of Helsinki, Finland): ERYTHROPOIETIC ACTIVITY OF SALINE WASHINGS OF BLOOD CELLS SUBJECTED TO LOW ATMOSPHERIC PRESSURE.

In order to test the role of blood cells in the formation of the erythropoietically active substance in blood subjected to low pressure *in vitro,* rabbit blood cells were suspended in physiological saline and the suspension was kept under a pressure of 50—100 mm Hg for 1—1½ hours. 7—15 cc of the saline were, after centrifuging, injected into normal test rabbits. As control another group of rabbits received injections of saline, in which normal rabbit blood cells had been suspended under normal pressure for 1—1½ hours. The injection of »low pressure saline» caused a moderate erythrocytosis in the recipient animals, while the injection of »normal pressure saline» was without effect. The difference between the two groups is statistically confirmed. In a second experimental group whole blood from normal rabbits was subjected to low pressure, plasma was removed, and the cells then suspended in physiological saline. The suspension was gently stirred, and after 20 minutes the saline was separated and injected into test rabbits. The injection caused an erythrocytosis of similar magnitude as in the former experimental group. Similarly prepared saline washings from blood kept under normal pressure were erythropoietically inactive. The number of experiments in this group is not sufficient to allow statistical treatment. Further investigations on the subject are in progress.

Hirvonen, L., H. Kalliola, T. Peltonen and A. Salovaara (Institute of Physiology, University of Turku, Finland): CHANGES IN THE AORTIC AND RIGHT INTRAVENTRICULAR PRESSURES AND IN THE ELECTROCARDIOGRAM OF THE CAT FOLLOWING ANGIOCARDIOGRAPHY.

Cats were anesthetized with an intraperitoneal Nembutal injection. Five cc of radiopaque substance were injected into the right atrium or ventricle with the automatic Gidlund's syringe. The aortic and right intraventricular pressures were recorded with Sanborn electromanometers simultaneously with an electrocardiographic lead. Immediately after the injection of the contrast substance the aortic pressure increased about 20 to 30 mm Hg and reached the maximum in 5 to 10 seconds. This was followed by a drop of about 20 to 30 mm Hg below the original value. Normal pressure was found after 3 to 5 minutes. The pressure changes in the right ventricle were generally parallel to those in the aorta. It was very often found that during the extrasystoles following the injection only the right heart was contracting. In the electrocardiogram the most striking change was a great increase in the R wave. None of these changes was present when the radiopaque was substituted with saline. Changes similar to those observed in the present study may explain the complications occurring in certain cases of human angiocardiography.

Hirvonen, L. and H. Lang (Institute of Physiology, University of Turku, Finland): OBSERVATIONS ON HYPOTHYROID HEART.

Heart muscle is sensitive to variations in the production of thyroid hormone. In the present study 40 albino rats were treated with radioactive iodine in order to perform radiothyroidectomy. Each of them received a single subcutaneous injection of 500 microcuries of I^{131} two to three months before the tests. The following determinations were performed on

these and on normal control animals: (*1*) The pulse rate was recorded electrocardiographically; the experimental animals were standing on two metal plates in a small wooden box. (*2*) The oxygen consumption was measured simultaneously from 5 or 10 animals by a closed circuit method in a room maintained at constant temperature. (*3*) The right atria were isolated and placed into an isolation chamber containing alkaline Locke's solution through which a rapid oxygen stream was forced. The beating rate of the atrial preparations was determined with a piezo-electrical recording system at various temperatures. (*4*) The effect of I^{131} on the thyroid gland was also verified by histological samples from the thyroid and by weight control of the animals.

It was found that the heart rate was practically the same in both rat groups. The oxygen consumption showed a diminution of about 7 per cent in hypothyroid animals. The spontaneous beating rate of the isolated atrial preparations of the I^{131}-treated rats was about 40 per cent lower than that of the normal animals. After injection of thyroxine the rate of the heart accelerates approximately equally *in situ* and in isolated state. In hypothyroid rats the difference between the beating rate of the heart *in situ* and that of the isolated atrial preparation can be explained on the basis of weaker resistance of hypothyroid heart muscle to artificial external conditions or by a compensating effect of the vegetative nervous system regulating the activity of the heart *in situ*.

Hisdal, B. and H. E. Refsum (The Central Institute of Industrial Research, and the University Institute for Respiratory Physiology, Ullevål Hospital, Oslo, Norway): A SIMPLE REFLECTOMETER FOR DETERMINATION OF HEMOGLOBIN OXYGEN SATURATION IN BLOOD.

The construction and calibration of a simple hemoreflector is described. The influence of the hemoglobin concentration on the amount of reflected light, and the use of $Na_2S_2O_4$ as desoxygenating agent is briefly discussed.

The hemoglobin oxygen saturation was determined both by reflectometry and spectrophotometry in 65 different blood samples. The mean differences between the reflectometric and spectrophotometric results in the ranges of percentage oxygen saturation 80—100, 60—80 and 0—60 were +0.6, —0.7 and +0.6 respectively, with standard deviations 1.0, 1.2 and 1.3 respectively. The reproducibility of the method was tested in two series of ten analyses each. In one series the mean percentage saturation, range and standard deviation was 83.2, 82.7—83.7 and 0.6 respectively, in the other 38.9, 38.0—39.9 and 0.3 respectively.

Högberg, B. and B. Uvnäs (Department of Pharmacology, Karolinska Institutet, Stockholm, and AB Leo, Helsingborg, Sweden): THE MECHANISM OF HISTAMINE RELEASE, I. *(cf.* Fernö, O., B. Högberg and B. Uvnäs, The Mechanism of Histamine Release, II).

Holmstedt, B. and F. Sjöqvist (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): DISTRIBUTION OF ACETOCHOLINESTERASE IN VARIOUS SYMPATHETIC GANGLIA.

The distribution of acetocholinesterase (AcChE) in various sympathetic ganglia of the cat has been studied with a modified thiocholine method (HOLMSTEDT 1957). The ganglia have been studied with and without inhibitors of butyrocholinesterase.

Cells with different intensity of staining have been counted in different ganglia. The influence of variations in incubation time, treatment with ammonium sulphide and the staining properties of various ganglia in different cats have been considered.

In general, three different types of ganglion cells can be distinguished, those showing high intensity of staining (Group I), those showing moderate to little intensity of staining (Group II) and those without any staining at all (Group III).

Cells of Group I have been found predominantly in the stellate ganglion, principally at the caudal end of the ganglion. There is a significant difference between the incidence of these cells in the superior cervical ganglion (also coeliac and superior mesenteric ganglion) on one hand and the stellate ganglion on the other. The approximate distribution of the different types is as follows:

In the stellate ganglion there are 7 % Group I, 7 % Group II and 85 % Group III cells, while in the superior cervical ganglion there are 0.5 % Group I, 20 % Group II and 80 % Group III cells.

The superior cervical ganglion shows the biggest variation between different cats. Minor morphological differences between different ganglia have also been found. The preparations stained by ammonium sulphide do not differ significantly from the others.

Incubation times below 30 minutes have given significantly lower values than those above 30 minutes, but no appreciable differences were found between the incubation times of 30, 40, 50 and 60 min. The staining of the cells in Group I is most dependent on the incubation time.

Holmstedt, B., Acta Physiol. Scand. 1957, in press.

Holmstedt, B. and R. Tham (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): A PHOTOMETRIC METHOD FOR DETERMINATION OF DIAMINE OXIDASE (DAO) ACTIVITY.

If DAO is allowed to act upon the diamine putrescine a cyclic compound, Δ-pyrroline, will be formed which in turn reacts with o-aminobensaldehyde to form a yellow compound.

These reactions have been taken as a starting point for a photometric method for determination of diamineoxidase. If a solution containing o-aminobensaldehyde, putrescine and a diamineoxidase preparation is incubated at 37° C a characteristic yellow colour is obtained. The intensity of the colour can be measured with a Beckman spectrophotometer.

The influence of pH and of the concentration of putrescine and of o-aminobensaldehyde on the reaction has been tested. The wave-length which gives a maximal extinction has been determined. The variation of the extinction with increasing time of incubation has been studied. On the basis of these investigations a standard procedure is suggested.

Simultaneously determinations of diamineoxidase in different dilutions have been carried out using this colorimetric method and the method described by AHLMARK in 1944.

Ahlmark, A., Acta Physiol. Scand. 1944. 9. suppl. 28.

Hougs, W. and C. Thorshauge (The Research Laboratory of GEA, Ltd., Copenhagen, and Institute of Medical Physiology, University of Copenhagen, Denmark): EXPERIMENTAL HYPERGLYCEMIA INDUCED BY MORPHINE SUPPRESSED BY CONTROLLED RESPIRATION.

Others have shown that when morphine is administered to rabbits in doses less than 10 mg/kg a progressive depression of respiration takes place. Maximal depression occurs after a dose of 10 mg/kg i.v.

Experiments presented here show that injection of morphine, 10 mg/kg, caused hyperglycemia in 10 rabbits; this hyperglycemia can be prevented and suppressed by controlled respiration.

In a series of experiments (3 rabbits) the oxygen saturation in arterial blood was measured after injection of morphine, 10 mg/kg. With decreasing oxygen saturation the blood sugar rose.

In another series (3 rabbits) oxygen saturation and blood sugar were measured before administration of morphine, after administration of morphine and a period of controlled respiration and after a period without controlled respiration.

It was found that oxygen saturation during controlled respiration was unchanged or increased and at the same time

the blood sugar remained constant. In the period without controlled respiration the oxygen saturation decreased and the blood sugar increased.

Iisalo, E. (Institute of Pharmacology, University of Turku, Finland): ON THE ENZYMATIC DESTRUCTION OF ADRENALINE AND NORADRENALINE IN SMOOTH MUSCLE TISSUES.

The method for the determination of enzymatic destruction of adrenaline and noradrenaline *in vitro* has been presented earlier (IISALO and PEKKARINEN 1954).

In addition to phosphate buffer blood has been used for the prevention of the auto-oxidation of adrenaline and noradrenaline (10 mg per cent) in tissue homogenate during the enzymatic oxidation under continuous oxygen stream at 37° C for 4 hours. In the smooth muscle tissue of the uterus of cattle the enzymatic oxidation of adrenaline and noradrenaline is prevented effectively by benzedrine (25—100 mg per cent) but only slightly by potassium cyanide (0.2—1 mg per cent per hour) or marsilid (5—20 mg per cent). In the smooth muscle of small intestine of cattle both marsilid and benzedrine prevent quite effectively the enzymatic destruction of adrenaline and noradrenaline. Potassium cyanide inhibits only slightly this oxidation.

These experiments indicate that in the smooth muscle tissue of the uterus and intestine amino oxidase oxidizes adrenaline and noradrenaline *in vitro*, but cytochrome oxidase only slightly.

Iisalo, E. and A. Pekkarinen, Acta Physiol. Scand. 1954. 31. suppl. 114. 25.

Ingelman-Sundberg, A., L. Lindgren, G. Rydén and F. Sandberg (Sabbatsbergs sjukhus, Department of Obstetrics and Gynaecology, and Royal Pharmaceutical Institute, Stockholm, Sweden): THE SPONTANEOUS MOTILITY IN DIF-

FERENT PARTS OF THE NON-PREGNANT UTERUS DURING THE SEXUAL CYCLE AND IN THE MENOPAUSE AND ITS CORRELATION TO THE ACTOMYOSIN CONTENT.

Muscle strips have been cut longitudinally and transversely from different parts of 85 non-pregnant uteri and studied qualitatively *in vitro* using Magnus-Kehrer technique. Eight main types of motility were found. The distributions of motility types were characteristic for the various parts of the uterus. In the corpus sinusoidal contractions were most common. In the isthmus single contractions with or without a »sphincterlike» pattern superimposed were prominent. In the cervix the spontaneous motility was poor. The »sphincterlike» contractions were only found in the isthmus.

The content of actomyosin and myosin was highest in the corpus and lowest in the cervix and no difference between the outer and inner layer could be demonstrated. No correlation was found between the content of the contractile proteins and the type of motility.

Ingelman-Sundberg, A., L, Lindgren, G. Rydén and F. Sandberg (Sabbatsbergs sjukhus, Department of Obstetrics and Gynaecology, and Royal Pharmaceutical Institute, Stockholm, Sweden): THE IN VITRO EFFECT OF OXYTOCICS, NORADRENALINE, ADRENALINE AND ACETYLCHOLINE ON ANATOMICALLY WELL DEFINED MUSCLE STRIPS FROM PREGNANT AND NON-PREGNANT HUMAN UTERI.

The pharmacological effects of the compounds tested have been studied on isolated muscle strips cut from the corpus and the isthmus of pregnant and non-pregnant human uteri, using Magnus-Kehrer technique in Tyrode solution modified according to GENELL (1937). The following parameters have been considered: *1.* change of the spontaneous motility pattern; *2.* change in tone; *3.* change in amplitude, and *4.* change in frequency of contraction.

The following oxytocics have been studied: Oxytocin (synthetic, as Syntocinon Sandoz, and native), Methergin, Ph 86, Ph 261, 1062 I.S., 621 I.S. and d- and l-sparteinesulphate.

It was observed that the response to the substances studied was different in different parts of the uterus. The response sometimes varied with the sexual phases, and the pregnant uterus as a rule was more sensitive than the non-pregnant uterus.

Among the observations concerning the effect of adrenaline, noradrenaline and acetylcholine the following may be mentioned. No difference in the action of adrenaline and noradrenaline could be demonstrated. The pregnant uterus was more sensitive than the non-pregnant to these substances, and the reverse effect was observed with acetylcholine.

Genell, S., Uterin- och vaginalmuskulaturens funktionella uppgifter i den icke gravida organismen. Thesis Lund 1937, p. 121.

Jalavisto, E. (Institute of Physiology, University of Helsinki, Finland): EFFECT OF REPEATED BLEEDINGS ON THE RATE OF REDUCTION OF METHAEMOGLOBIN IN RABBIT ERYTHROCYTES.

The rate of methaemoglobin reduction (MRR, per cent/1 hour) in washed rabbit erythrocytes pretreated with 1 per cent sodium nitrite, is enhanced by repeated bleedings (MATTHIES *et al.* 1953), by exposure of the rabbits to low pressure and by injections of adrenaline (JALAVISTO 1956, 1957). The increased MRR has been ascribed to the presence of reticulocytes (MATTHIES *et al.* 1953). A simple calculation shows, however, that even if the reticulocytes would reduce all methaemoglobin contained in them to haemoglobin during the experimental period (one hour), the mean MRR found in the experiments would require a higher percentage of reticulocytes than has actually ever been recorded.

If blood is stored for 6—24 hours the MRR decreases considerably. However, even in the stored samples with very slow

reduction, the red cells from anaemic rabbits reduce methaemoglobin at a higher rate than do those of the controls.

The MRR in erythrocytes from both anaemic and normal rabbits can be greatly enhanced by incubation of the blood samples with adenosine. The difference between anaemic and control rabbit cells is still present after pretreatment with adenosine suggesting that the difference is not due to higher concentration of ATP in the anaemic cells.

Jalavisto, E., Abstr. Comm. XXth Congr. Physiol., Brussels, 1956.
Jalavisto, E., Ann. Exp. Med. Biol. Fenn. 1957 (in press).
Matthies, H., F. Jung and K. Onnen, Dtsch. Gesundheitswesen 1953. *8*. 1562.

Jäntti, K. (Institute of Physiology, University of Turku, Finland): STUDIES ON CONSENSUAL EYE REACTIONS IN RABBIT EYE.

In this work an investigation is made into the effects of the thermal irritation on the aqueous of living rabbit eyes.

In fundamental experiments usually a strong Tyndall phenomenon of the irritated eye was noticed, when 43.5° C was applied for 3 hours. The same effect was often seen also in the aqueous of contralateral, nón-irritated eye (consensual reaction).

A consensual Tyndall phenomenon appeared in 32 cases in 75 experiments. The effects of the drugs mentioned below on the occurrence of the consensual reaction were further investigated. The following results were obtained in 75 experiments with each of the drugs:

	Consensual reactions
Hydrocortisone (topical in the non-irritated eye) ..	12
pilocarpine (topical in the non-irritated eye)	26
homatropine (topical in the non-irritated eye)	29
neosynephrine (topical in the non-irritated eye)	42
dibenamine (given intravenously)	13
blocking of the ciliary ganglion of the irritated eye with xylocain	24

Kaada, B. R. and H. Ursin (Anatomical Institute, University of Oslo, Norway): SUBCORTICAL MECHANISMS IN THE »ATTENTION» RESPONSE INDUCED FROM THE AMYGDALA IN CATS.

Stimulation of parts of the amygdala through implanted electrodes in unanesthetized cats results in a typical »attention» or searching behavior similar to that obtained from the medial prefrontal and cingular cortex. In a previous study (JANSEN, ANDERSEN and KAADA 1955/56), it was shown that the prefrontal »attention» response was abolished by lesions which included the anterior basal part of the internal capsule on the same side, or when parts of the intralaminar nuclei of the thalamus (notably n. centralis medialis, n. paracentralis, and n. centralis lateralis) were destroyed bilaterally.

Similar experiments with the combined stimulation-ablation technique have been performed in order to determine which subcortical structures are necessary for the elicitation of the amygdaloid »attention» response. The reaction was found to persist after electrolytic lesions of the same structures which abolished the prefrontal response. Neither was it affected after extensive bilateral lesions of the following subcortical structures:

Thalamus: the midline and intralaminar nuclei (including n. centralis medialis, n. paracentralis and n. centralis lateralis), centrum medianum, n. dorsomedialis, the anterior group of nuclei, the rostral part of n. reticularis, n. ventralis pars posterolateralis and pars posteromedialis and n. lateralis posterior.

Hypothalamic and septal areas: the dorsal portion of the hypothalamus throughout its entire length, the rostral parts of the ventral hypothalamus (including n. ventromedialis); most of the septal nuclei.

Mesencephalon: the dorsal half of the tegmentum including the dorsal half of the periaquaeductal gray at the level of the rostral colliculi; a large part of the reticular substance; substantia nigra and the red nuclei.

It is concluded that the amygdaloid »attention» response is effectuated either by connections to rather widespread subcortical areas not eliminated *in toto* in our experiments, or that the response is dependent on a rather small crucial area not hit in the ablation experiments. Further studies are in progress.

Jansen Jr., J., P. Andersen and B. R. Kaada, Yale J. Biol. & Med. 1955/56. 28. 331.

Kaada, B. R. and H. Ursin (Anatomical Institute, University of Oslo, Norway): FURTHER LOCALIZATION OF BEHAVIORAL RESPONSES ELICITED FROM THE AMYGDALA IN UNANESTHETIZED CATS.

On the basis of stimulation experiments a functional localization within the different nuclei of the amygdala has previously been suggested (KAADA, ANDERSEN and JANSEN 1954). Various autonomic and immediate somatomotor responses were evoked mainly from the phylogenetically old anteromedial division, whereas stimulation of the phylogenetically younger basolateral division resulted in a typical »attention» or »searching» response characterized by initial arrest of current activity, dilatation of the pupils, and quick glancing or searching movements to the contralateral side. This reaction might be associated with fear, anger and fury.

GLOOR (1955) was inclined to conclude that there was no functional organization within the amygdala. However, in the present study, an analysis of the responses from more than one hundred additional electrode sites in 45 cats have supported our previous assumption of a functional localization within this nuclear complex, although some overlapping of the areas yielding the various effects exists.

(*1*) The »attention» response was induced from the basolateral division of the amygdaloid complex and also from an area extending medially through the region of the central

nucleus and into the internal capsule. This medial extension of the responsive area possibly corresponds to the course of the »c«-bundle described by FOX (1940). Some responsive points were located in the anterior amygdaloid area, almost none in the periamygdaloid cortex. The EEG arousal produced by amygdala stimulation seemed to parallel the behavioral »attention« response.

(2) Flight and anger reactions, both associated with the »attention« response, were induced from two separate zones running approximately parallel in a medio-dorso-caudal direction. Flight and fear resulted from excitation of an area extending from the rostral part of the lateral nucleus through the region of the central nucleus and into the internal capsule. Anger and growling were elicited from more ventral and caudal parts, mainly from the basal nucleus. Medially the two zones partly overlap in the area of the central nucleus and they can both be traced in to the internal capsule.

(3) Sniffing, often associated with the »attention« response, was obtained from rather widespread areas of the amygdala, most frequently from the rostral portion of the lateral nucleus. Some positive points were found, among negative ones, in the region of n. centralis, the anterior amygdaloid area and in the rostral portion of the pyriform cortex.

(4) Sites yielding autonomic responses (pilo-erection, salivation, micturition and defecation) were almost entirely located within the anteromedial division of the amygdala.

A comparison of these data with those recently published by MAGNUS and LAMMERS (1956) reveals good agreement with regard to the localization of the various types of responses elicited from the amygdala.

Fox, C. A., J. Comp. Neurol. 1940. 72. 1.
Gloor, P., EEG Clin. Neurophysiol. 1955. 7. 223.
Kaada, B. R., P. Andersen and J. Jansen Jr., Neurology. 1954. 4. 48.
Magnus, O. and H. J. Lammers, Folia psychiat., neurol. et neurochir. neerl. 1956. 59. 555.

Kågström, E. (Serafimerlasarettet, Department of Neurosurgery, and the Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): EFFECTS OF SEROTONIN AND NORADRENALINE ON CEREBRAL AND MUSCULAR BLOOD FLOW IN RABBITS.

The cerebral arteries are generally considered to be less sensitive to vasoactive substances, especially the vasopressor drugs, than arteries in other vascular areas. The injection of adrenaline or noradrenaline into the carotid artery, in doses that have only minimal transient effects on the systemic blood pressure, usually has little effect on the cerebral blood flow. Some investigators have reported a slight vasoconstriction after the injection of noradrenaline. Serotonin, when applied on the cerebral surface, has been found to cause a constriction of the pial vessels (BRUN 1950). The relative sensitivity of blood vessels in different peripheral areas to several pressor agents varies. GINZEL and KOTTEGODA (1953) found that serotonin was a more powerful constrictor of the pulmonary vessels of the dog and the cat and of the rabbit's ear than noradrenaline and adrenaline, whereas the latter substances were more powerful constrictors of the hindleg vessels of the dog and the cat and of the renal vessels of the cat than serotonin.

The purpose of the present investigation was to compare the effect on the cerebral and the muscle circulation of serotonin and noradrenaline. Fifteen rabbits with chloralose-urethane anaesthesia were used. The blood flow in the internal carotid artery was measured with a photoelectric drop-counter. The substances were injected into the internal carotid artery distally to the drop-chamber. The injection of 1—5 μg of serotonin was followed by a 30—60 per cent decrease in the blood flow of 4—10 minutes' duration. The injection of similar doses of noradrenaline produced only a 10—20 per cent decrease in the blood flow.

To study the effect of these substances on the hindleg vessels in the rabbit, the venous outflow from the leg muscles was measured in the femoral vein with a similar method. The injection of 1—5 μg of noradrenaline into the femoral artery

caused a 40—60 per cent reduction in the blood flow. The injection of similar doses of serotonin was followed by a 20—40 per cent decrease only.

Brun, G. C., Acta Pharmacol. et Toxicol. 1950. 6. 74.
Ginzel, K. H. and S. R. Kottegoda, Quart. J. Exper. Physiol. 1953. *38*. 225.

Kallio, I. V. I. and E. O. J. Tala (Mental Hospital of Turku and Institute of Pharmacology, University of Turku, Finland):
ON THE CHANGES IN PLASMA 17-HYDROXY-CORTICOSTEROID LEVELS AFTER ELECTROSHOCK THERAPY.

The effect of electroshock on the adrenals has earlier been studied by *e. g.* PEKKARINEN *et al.* (1952) and BLISS *et al.* (1954). In this study the changes of plasma 17-OHCS have been determined in 15 psychiatric patients after electroshock therapy, in 5 patients after electrostimulation without convulsions and in 6 patients without electroshock. The patients were not given any premedication. To eliminate the influence of diurnal rhythm on plasma 17-OHCS the electroshocks were given at the same time, at 9 a. m. Heparinized venous blood was used and the samples were centrifuged immediately after the withdrawal. The 17-OHCS in plasma have been determined according to the method of PETERSON and WYNGAARDEN (1955).

The mean levels of plasma 17-OHCS in patients subjected to electroshock were 19.6 μg % at 8.50 a.m., 29.4 μg % at 9.15 a.m., 25.8 μg % at 10.45 a.m. and 17.5 μg % at 12 o'clock. The electroshock caused a considerable rise in the plasma levels of 17-OHCS. The reaction was apparently rapid and of short duration. The mean plasma level of 17-OHCS 3 hours after the electroshock was already lower than the mean level before the shock. In the patients with electrostimulation without convulsions the mean levels of plasma 17-OHCS were 16.9 μg % at 8.50 a.m., 22.8 μg % at 9.15 a.m., 16.5 μg % at 10.45 a.m. and 11.3 μg % at 12 o'clock. Hence a rise was observed also after electrostimulation without convulsions. In the control group

without electroshock in the same circumstances the mean levels of plasma 17-OHCS were 13.9 μg % at 8.50 a.m., 16.0 μg % at 9.15 a.m., 14.1 μg % at 10.45 a.m. and 15.6 μg % at 12 o'clock. The rise was not significant. After surgical procedures (FRANKSSON and GEMZELL 1954, FRANKSSON *et al.* 1954, VIIKARI and THOMASSON 1957) the rise of plasma levels of 17-OHCS has been greater and more uniform in different cases and of much longer duration than after electroshock.

Bliss, E. L., C. J. Migeon, D. H. Nelson, L. T. Samuels and C. H. Hardin-Branch, Arch. Neurol. & Psychiat. 1954. *72.* 352.

Franksson, C. and C. A. Gemzell, Acta chir. Scandinav. 1954. *106.* 24.

Franksson, C., C. A. Gemzell and U. S. von Euler, J. Clin. Endocrinol. 1954. *14.* 608.

Pekkarinen, A., H. Hakala and K. Hyppönen, Acta endocrinol. 1952. *10.* 167.

Peterson, R. E. and J. B. Wyngaarden, Ann. New York Acad. Sc. 1955. *61.* 297.

Viikari, S. J. and B. H. Thomasson, Acta endocrinol. 1957. *24.* 361.

Karlog, Ole (Royal Veterinary and Agricultural Institute, Copenhagen, Denmark):

BIOTRANSFORMATION OF PARATHION.

Karvonen, M. J. and N. Räihä (Department of Physiology, Institute of Occupational Health, Helsinki, Finland):

PERMEABILITY OF PLACENTA TO MONOSACCHARIDES.

A solution of various monosaccharides was infused into the maternal circulation, or injected into the umbilical vein, and repeated samples were taken from the maternal and foetal circulation. The permeability was expressed as apparent net transfer rate (ANTR), *i. e.*, as a change of the level of the sugar in the foetal blood as calculated per minute per a maternal-foetal gradient of unity. The permeability decreased approximately in the following order: glucose — mannose — galactose — d(+)xylose — l(+)arabinose — d(—)ribose — l(—)xylose — rhamnose — l(—)fucose — sorbose — fructose

— d(—)arabinose. The order resembles that previously demonstrated for the permeability of the human red cell. It was shown with d(—)xylose that its ANTR was indirectly proportional to its level on the side of the higher concentration. This also agrees with the kinetics of the permeability across the erythrocyte membrane, being typical of the kinetics of a carrier transfer.

Kenedi, T., H. Lagerlöf, G. Perman and M. B. Rudewald (Serafimerlasarettet, Department of Medicine, Stockholm, Sweden): MECHANISMS INVOLVED IN THE ACID NEUTRALIZING PROCESS IN THE DUODENUM OF MAN. — METHOD AND SOME PRELIMINARY RESULTS.

In order to study the acid neutralization process in the duodenum in different clinical conditions a mixture containing 0.1 N hydrochloric acid, 6 % dextran and 10 % heavy water is instilled into the stomach through a double lumen catheter. One of its lumens opens with several holes just above the pylorus and the other in the same way below the duodenojejunal junction. In recent experiments also polyethylene glycol was added to the test mixture as a test substance.

Samples of the gastric contents are obtained at regular intervals at the same time as calculated losses to duodenum are compensated. The jejunal contents are collected continuously. pH, dextran, heavy water, amylase, bicarbonate, H^+, Cl^-, bilirubin index and polyethylene glycol are determined in all samples.

The part of the instilled mixture, which appears in different samples, is given by its content of dextran and polyethylene glycol. Water absorption may be calculated from the relation between the concentrations of dextran and heavy water. The following factors can be calculated for each time period: Total volume of gastric contents, gastric secretion of water, gastric absorption of water, net gain of H and Cl ions in the gastric contents, volume and total amount of H and Cl ions entering the duodenum, total duodenal secretion, total duodenal water

absorption, total duodenal secretion of bicarbonate, net disappearence of total chlorides. The total volume of pancreatic juice can be estimated and compared with the secretion after secretin. The possible liberation of pancreozymin can be judged by the amylase secretion, the liberation of cholecystochinin by the secretion of bile pigments.

In accordance with the results of SCHOLER and CODE (1954) the absorption of water has turned out to be considerable. It is of such a magnitude in the stomach and in the duodenum that it has to be taken into account in appraising the secretion.

Pancreatic secretion probably plays an important role in the conglomerate of factors regulating the acid neutralizing process in the duodenum not only directly but also because of its influence on the pH of the duodenum and consequently on the emptying of the stomach.

In the absence of pancreatic secretion complete neutralization has been attained by extreme retardation of the emptying of the stomach.

When the pH of the jejunal samples is about 4 or even lower the amylase is rapidly destroyed. Consequently measurable amounts of amylase are obtained only when the pH is higher and the neutralization is more complete. To avoid inactivation of the amylase during the storage a small quantity of every jejunal sample is immediately buffered to pH 6.8.

Judging by the amylase amounts obtained the main incitement to pancreatic secretion in our experiments is the liberation of secretin. If any liberation of pancreozymin occurs it is of minor importance.

Scholer, J. and C. F. Code, Gastroenterology 1954. 27. 565.

Kobinger, W. (Leo Pharmaceutical Products, Pharmacological Laboratory, Copenhagen, Denmark): DIFFERENTIATION OF THE SEDATIVE ACTION OF SEROTONIN (5-HYDROXYTRYPTAMINE) AND RESERPINE ON MICE.

The discovery that reserpine liberates serotonin in various tissues, especially brain, has raised the question whether the action of reserpine is mediated through the liberated serotonin.

The experiments to be described were performed by the photocell-count method of DEWS (1953). The spontaneous activity of groups of 5 mice was recorded for 30 minutes; serotonin in various doses and d-methylamphetamine (pervitin) in a constant dose of 3.3 mg/kg were injected simultaneously i.p. 5 minutes before the beginning of the recording period; reserpine in various doses was injected i.p. 2 hours before d-methylamphetamine.

Under these experimental conditions serotonin was able to counteract the increased motility after d-methylamphetamine. This sedative action was dependent on the serotonin dose; a complete suppression of the d-methylamphetamine action was seen with 5 mg/kg serotonin.

Reserpine, on the contrary, in doses up to 20 mg/kg was not able to prevent the hyperactivity induced by d-methylamphetamine.

These results show no resemblance between the sedative action of reserpine and parenterally administered serotonin.

Dews, P. B. Brit. J. Pharmacol. 1953. *8*. 46.

Koefoed-Johnsen, V. (Institute of Zoophysiology, University of Copenhagen, Denmark): THE EFFECT OF g-STROPHANTHIN (OUABAIN) ON THE ACTIVE TRANSPORT OF SODIUM THROUGH THE ISOLATED FROG SKIN.

To the isolated surviving frog skin bathed on both sides with Ringer's solution, g-Strophanthin was added to a concentration of 10^{-6}M to the solution bathing the inside of the skin. Both potential and short circuit current decreased within a short time to very low values. The relationship between the measured $\triangle$ Na — the difference between the influx and efflux of Na — and the measured shortcircuit current was not disturbed, *i. e.* $\triangle$ Na equalled the current. Under the influence of g-Strophanthin K leaked out of the cells into the inner solution. The results are discussed in the light of the theory

about the origin of the frog skin potential, which was put forward at the XX. International Physiological Congress in Brussels 1956 by Ussing and Koefoed-Johnsen.

Krayer, O. and M. K. Paasonen (Department of Pharmacology, Harvard Medical School, Boston, Mass., USA): DIRECT CARDIAC ACTION OF RESERPINE.

KRAYER and FUENTES (1956) have shown that reserpine increases the heart rate, when injected in doses of 10 μg to 5 mg into the blood volume of 1 liter of the dog heart-lung preparation (HLP). Higher doses are less effective. The positive chronotropic action has been studied in greater detail. The effect of a single dose develops gradually and is long-lasting. Evidence has been obtained that this reserpine-induced heart rate increase may be the consequence of noradrenaline (NA) release from the heart. That reserpine depletes the NA content of rat heart *in vivo* has already been reported by PAASONEN and KRAYER (1957); other Rauwolfia alkaloids, such as raunescine, isoraunescine, recanescine and rescinnamine, have the same effect.

In the HLP in a state of myocardial failure, reserpine administration leads to a positive inotropic as well as to a positive chronotropic effect. Further, veratramine, which selectively antagonizes the chronotropic effect of adrenaline (A) and NA, only abolishes the reserpine-induced tachycardia, but not the improvement of the work capacity.

We have measured the catechol amine concentration in the right auricle and left ventricle during the reserpine-induced tachycardia in the HLP. The standard dose of reserpine was 3 mg. The extracts were assayed on the cat blood pressure and on the isolated chicken rectal caecum. With regard to NA, a marked decrease in concentration appeared, after the heart had been exposed to reserpine for two hours or more. No clear-cut changes occurred in the A content.

When dogs were pretreated with reserpine (0.5 mg/kg) three and two days prior to using them for the setting up of a

HLP, reserpine injection into the HLP did not increase the heart rate. No NA was found in these hearts. It is probable that reserpine was ineffective in the HLP from these dogs because the pretreatment of the intact animals depleted the NA stores.

In the dog HLP 5-hydroxytryptamine, known to be released from tissues by reserpine, had little, if any, effect upon the heart rate when given as continuous infusion in doses from 0.1 to 100 μg/min.

Krayer, O. and J. Fuentes, Fed. Proc. 1956. *15*. 709.
Paasonen, M. K. and O. Krayer, Fed. Proc. 1957. *16*. 326.

Krog, J. and P. F. Scholander (The University Institute for Experimental Medical Research, Ullevål Hospital, Oslo, and Institute of Zoophysiology, University of Oslo, Norway): COUNTER CURRENT VASCULAR HEAT EXCHANGE, WITH SPECIAL REFERENCE TO THE ARTERIO-VENOUS BUNDLES IN SLOTHS.

In the sloth, a few other terrestrial mammals, and several aquatic mammals, the limbs and tail are provided with arterio-venous bundles (retia) where twenty to forty, or sometimes several hundred, small arteries and veins run parallel and intermingled. Obviously heat exchange must take place in such a structure. The basic temperature relations in a simple counter current exchange system have been described and verified on a physical model. A striking feature of such a system is the poor conduction of heat and the consequent steep temperature gradient along the line of flow. Temperature measurements in the rete of the sloth revealed gradients sometimes as large as one degree per cm, *i. e.*, some thirty times steeper than in the human arm. The gradient immediately decreased when the venous return was reduced, proving the existence of A-V heat transfer. Legs and arms developed steep subcutaneous gradients upon cooling of the body. It took some four hours to rewarm a moderately chilled limb to normal temperature. Two other tropical animals (coati and white-faced monkey), without retia, rewarmed their arms after chilling five times faster. Hot wire

measurements indicated that flow often decreased in the arm rete when a sloth was chilled. At the same time the rete gradient steepened. The sloth is a temperature-sensitive animal which just barely keeps warm in the tropics, and the retia in sloths and other mammals are interpreted as structures which conserve the body heat at the expense of cooling the limbs.

Lagergren, B. (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): IN VITRO RELEASE OF HISTAMINE FROM THE CAT'S SKIN PRODUCED BY SOME HISTAMINE LIBERATORS.

The histamine release from finely minced skin of the cat was investigated. Mostly the abdominal skin was used. It was cut into thin slices and very small amounts of histamine were lost by this procedure. Equal portions of skin were then incubated with Tyrode's solution containing various amounts of liberator. The spontaneous loss of histamine was small. The histamine released was tested biologically on atropinized guinea-pig ileum. Also the total amount of histamine of the skin was determined.

The influence of time, temperature, pH, concentration of liberator etc. on the release was tested.

The liberators used were compound 48/80 and extracts from Ascaris and jelly-fish. Their mode of action will be discussed.

Lagerlöf, H. and G. Perman (Serafimerlasarettet, Department of Medicine, Stockholm, Sweden): THE STABILITY OF AMYLASE IN THE DUODENAL JUICE.

Pancreatic amylase has its pH optimum around 6.8—7.2. At pH 4—5 and below, it is rapidly destroyed. In normal persons the pH level in the duodenum is around 7 and consequently amylase is stable. In cases of duodenal ulcer, however, pH values of 4 and less are found, resulting in a rapid destruction of the amylase. This may be the explanation of the belching and diarrhoea often found in these cases.

Lähdevirta, J., R. S. Piha and A. Raina (Institute of Physiology, University of Helsinki, Finland): CHANGES IN PLASMA AND RED CELL PYRUVIC ACID IN RABBITS RENDERED ANAEMIC BY REPEATED BLEEDINGS.

In a previous paper it was shown that changes in the concentration of ascorbic acid, dehydroascorbic acid and free amino acids of plasma and red cells occur during reticulocytosis due to repeated bleedings (PIHA 1956). The present report deals with the behaviour of pyruvic acid in haemorrhagic anaemia combined with simultaneous hypo- or hyperproteinaemic states.

From thirteen rabbits used seven were referred to as »anaemic-hypoproteinaemic», three »anaemic» and three »anaemic-hyperproteinaemic». Anaemia was produced by removing blood about 1 per cent of bodyweight on four successive days. The blood volume lost was replaced in the first group with the corresponding volume of saline and in the second group with that of normal plasma. The rabbits of the third group received intravenously back their own plasma and, in addition, a considerable amount of foreign plasma. By means of these pretreatments the haemoglobin content was reduced to about 40 per cent of the normal and the plasma proteins were adjusted to approximate levels of 85, 100 and 110 per cent of the initial in the groups mentioned above. Pyruvic acid was determined at intervals during the bleeding period and the recovery.

The results appear to indicate that in each of the rabbit groups a conspicuous increase in plasma and red cell pyruvic acid is found. The initial *plasma* pyruvic acid concentration in the »anaemic-hypoproteinaemic», »anaemic» and »anaemic-hyperproteinaemic» rabbits were averaged at 2.9, 2.9 and 2.3 mg/100 ml whilst the maximum increases were about 100, 70 and 60 per cent of the initial, respectively. The pyruvic acid content remained above the normal for about two weeks. The maximum rises of the *red cell* pyruvic acid in the corresponding groups were approximately 100, 110 and 110 per cent of the mean initial values, which were estimated at 2.1, 1.9 and 1.8 mg/100 ml. The peak fell on the fifth day of the experiment, after which the pyruvic acid decreased steeply reaching the normal

level on the fifteenth day. A correlation between the changes of red cell pyruvic acid and the reticulocytosis was found.

From the results it appears that reticulocytes contain more pyruvic acid than the mature erythrocytes. Paying attention also to the fact that in other conditions when blood regeneration is increased, *e.g.*, under reduced atmospheric pressure (TEPPERMAN and TEPPERMAN 1948), in haemolytic disorders (ALLIBONE 1948), in new-borns (TALLQVIST 1952) and in experimental hypoxia induced by carbon monoxide (VITACCA and PAGANO 1955), increased blood pyruvic acid values have been observed, it is suggested that pyruvic acid participates in a reaction sequence which is coupled with the haemoglobin regeneration.

Allibone, E. C., Arch. Dis. Childhood 1948. *23*. 7.
Piha, S., Ann. Acad. Sci. fenn. Ser. A II. 1956. Nr 80.
Tallqvist, H., On pyruvic acid in fetuses, children and adults with special reference to the role of prematurity. Hämeenlinna. 1952. 75 pp.
Tepperman, J. and H. M. Tepperman, J. Clin. Invest. 1948. *27*. 176.
Vitacca, L. and R. Pagano, Fol. med., Nap. 1955. *38*. 383.

Landgren, S. (Department of Physiology, Veterinärhögskolan, Stockholm, Sweden):

CORTICAL RECEPTION OF AFFERENT IMPULSES FROM THE TONGUE OF THE CAT.

The activity of single cells was recorded with microelectrodes inserted in the cortical tongue-projection area. Cellular responses were evoked by tactile, thermal, gustatory or electrical stimuli applied to the tongue.

Cortical cells responding »specifically» to tactile stimulation of the tongue were found most frequently. These cells were discharged with a short latency (5 msec to electrical stimulation of the tongue). They showed a typical pattern of discharge consisting of an initial burst of spikes on the rising phase of the primary cortical evoked potential, a silent period during the positive wave following the initial, negative primary potential and a long-lasting delayed discharge correlated with a late negative wave. This pattern was observed in response to tactile as well as to electrical stimuli. The »specific» touch cells were

concluded to be primary cortical cells and to belong to the group of large pyramidal cells of layers III and V. The receptive field on the tongue belonging to single cortical touch cells was investigated (COHEN, LANDGREN, STRÖM and ZOTTERMAN 1957).

Cortical cells responding »specifically» to thermal or to gustatory stimuli were also found. The shortest latency (15 msec) shown by a specific cold cell was 3 times longer than that of the touch cells, a relation which also holds for the conduction velocity of the two types of afferent fibres. The latency, duration and frequency of the cortical cold cell response were observed to be dependant on the intensity of the cooling of the tongue.

The cortical taste cells observed responded to more than one quality of taste. A group of these cells was, however, »specific» to gustatory stimuli and was not discharged by tactile or thermal stimulation of the tongue.

In addition to the »specific» cortical cells a group of cells which were discharged via afferent fibres subserving different sensory modalities was found. Thus a group of cortical cells responded to cooling and to tactile stimulation of the tongue and another group to taste and to touch. These cells showed a frequent and long-lasting response to thermal or gustatory stimuli and a relatively weak response to tactile stimulation. The latency of their discharge was long (about 100 msec).

Finally a number of cortical cells could be discharged by tactile as well as by thermal and gustatory stimuli.

Cohen, M. J., S. Landgren, L. Ström and Y. Zotterman, Acta Physiol. Scand. 1957. *40*. Suppl. 135.

Larsson, S. (Department of Physiology, Veterinärhögskolan, Stockholm, Sweden): DIET PREFERENCES IN EXPERIMENTAL OBESITY.

The preference for different diets has been studied in mice made obese by a single injection of goldthioglucose. The animals were allowed free selection of three different diets. It was found that most animals could develop obesity on a

standard diet which had low fat content. In the other cases it was necessary to give the animals free choice of the diets in order to get significant increase in weight. The preference for fat and carbohydrate was found to vary considerably among the different obese animals. In most cases no carbohydrate was eaten when the animals were gaining weight. On standard diet the obese mice kept a fairly constant weight, but on free selection sudden weight losses were frequently observed. Histological examinations of the liver in these cases revealed marked fatty degenerations.

These and other findings on experimental obesity are discussed in relation to the current views of treating obesity in man by dietary means.

Lennox, M. A. (Institute of Neurophysiology, University of Copenhagen, Denmark): RESPONSES IN SINGLE OPTIC TRACT FIBERS OF CAT TO MONOCHROMATIC LIGHT: CORRELATION WITH CONDUCTION VELOCITY.

In chloralose-urethane anesthetized cats, a just supramaximal electrical stimulus was applied to one optic nerve just behind the intact eye and the response recorded with a gross and an immediately adjacent glass capillary microelectrode from the contralateral optic tract. The responses recorded with the microelectrodes had the characteristics of single fiber responses (TASAKI, POLLEY and ORREGO 1954) and the conduction velocity could be calculated from the latency and the measured distance between stimulating and recording electrodes. Responses were then recorded in these same fibers by flashing the intact eye with light which could be varied independently with respect to intensity, color, duration and frequency. The two colors used, blue and red (interference filter with a half intensity band width of 25 mμ and a peak transmittance at 445 mμ for blue; glass filter transmitting light above 600 mμ for red) were adjusted to equal brightness; the maximum intensity with the red filter was about 400

μW/cm^2 and the intensity of the blue flash was adjusted by the addition of neutral filters to evoke a retinogram of equal amplitude using 33 msec flashes at the rate of one per second after at least two hours of dark adaptation.

As in frog (HARTLINE 1938) the responses to light evoked in single optic tract fibers in cat were of three types, on, off and on-off, and unlike retinal units (KUFFLER 1953, GRANIT 1955) the response type of any one fiber was a fixed characteristic.

The on responses, whether of on or of on-off fibers, were different for different units according to the color of the stimulating light, whether red or blue, and these differences were related to the conduction velocity along the fiber as judged by the latency of its response to electrical stimulation. Fibers with slow conduction velocity responded more actively to blue than to red flashes, in that the response to blue had more spikes, a higher frequency and a latency about the same as to red. Fibers with fast conduction velocity responded to red with a shorter latency than to blue, with more spikes and with nearly as high a frequency.

Half the off fibers were extremely sensitive to the brightness of the light but not to its color and there was no correlation with conduction velocity. The number of spikes per unit time increased sharply with increasing amounts of stimulating light, whether this was accomplished by increasing the intensity of the light or its duration. Blue and red lights of equal brightness, though of very different intensity, evoked the same response pattern.

In the cat the majority of optic tract fibers were off fibers, and these appeared to be the only units allowing discrimination of the brightness of light. The on responses differed according to the color of the light, and these differences were correlated with the conduction velocity along the fiber.

Granit, R., Receptors and Sensory Perception, New Haven, Yale University Press. 1955. 369 pp.

Hartline, H. K., Am. J. Physiol. 1938. *121*. 400.

Kuffler, S. W., J. Neurophysiol. 1953. *16*. 37.

Tasaki, I., E. H. Polley and F. Orrego, J. Neurophysiol. 1954. *17*. 454.

Liljedahl, S. O., O. Mattsson and B. Pernow (Karolinska Sjukhuset, Departments of Surgery and Roentgenology and Laboratory of Clinical Physiology, Stockholm, Sweden): EFFECT OF SUBSTANCE P ON THE INTESTINAL MOTILITY IN MAN.

Liljestrand, A. (Södersjukhuset, Department of Internal Medicine IV, Stockholm, Sweden): NEUROMUSCULAR TRANSMISSION AND POTASSIUM DISTURBANCES IN HUMAN SUBJECTS.

Marked weakness which in part is due to impaired neuromuscular transmission is seen in states both with low and with high ratios of intracellular to extracellular potassium in the muscles. The effect of intraarterially injected acetylcholine on neuromuscular transmission shows the ease of depolarization of the tested muscles and may indicate the level of the resting muscle membrane potential. With this method an increase in the ease of depolarization was found concomitant with a probable decrease of the ratio intracellular to extracellular potassium concentration (GROB *et al.* 1957 a, b). This was attributed to a reduction in the resting muscle membrane potential. Concomitant with an increase in the concentration ratio of potassium there was a decrease in the ease of depolarization attributable to an increase in the resting muscle membrane potential. Although these results seem to support the hypothesis of the fundamental importance of the potassium ratio for the membrane potential, the complete lack of knowledge of the potassium movement or the lack of this movement in certain diseases makes such an explanation doubtful (Liljestrand 1957).

Grob, D., R. J. Johns and Å. Liljestrand, Am. J. Med. 1957 a, in press.
Grob, D., Å. Liljestrand and R. J. Johns, Am. J. Med. 1957 b, in press.
Liljestrand, Å., Opuscula Medica 1957, in press.

Lindblom, U. F. (Department of Physiology, Karolinska Institutet, Stockholm, Sweden): FUNCTIONAL ORGANIZATION WITHIN THE PERIPHERAL SENSORY UNIT FOR TOUCH.

Mechanical pulses from a loudspeaker transmitted by a blunt stylus were applied directly to the skin on the hindlegs of decerebrate toads. Single spike recording was made from dorsal root filaments. The movements of the stimulating stylus were recorded by means of a capacitance meter of the high-frequency phase-sensitive type. The moments when the stylus made and broke contact with the skin were indicated by small condenser discharges. The time course and spatial distribution of the displacement of the skin surface could be determined by using this device and double stimuli and also by means of a stroboscope. The amplitude of the mechanical pulse was varied between 0 and 600 μ.

Pulses of short duration (2—3 msec) initiate one impulse in the dorsal root fibre at a certain minimal value of the amplitude of displacement of the skin (threshold value). When the stimulus amplitude is increased above threshold still only one impulse is evoked per stimulus but the latency of the response is reduced by 1—5 msec. Stimuli of prolonged duration initiate bursts of impulses (2—20). The receptive field of a single dorsal root fibre usually consists of 3—12 sensitive spots, most often located on warts, within an area about 3—8 mm in diameter. The threshold is different at different sensitive spots within the same receptive field. Most spots have their thresholds within the range of 30—170 μ displacement of the skin. No definite correlation has so far been found between the position of a spot within the field and its threshold value. The shortest latency of the response also varies from one spot to another. The results indicate that these latency variations are not correlated to the threshold values. Small receptive fields (2 mm in diameter) may be found in certain regions, *e.g.* the tips of the digits where warts are missing. The threshold of these units is low and the sensitivity is not localized to certain spots.

In a series of experiments the threshold was determined

at different intervals after an impulse had been initiated (*i*) from the same spot, (*ii*) from another spot innervated by the same dorsal root fibre or (*iii*) by antidromic electrical stimulation of the dorsal root. In each case the conditioning impulse is followed by a period of a few msec during which stimulation with a pulse amplitude of 300—600 μ is unable to initiate a second impulse. During a subsequent period which may be as long as 300 msec a test impulse can be elicited but only if the amplitude of the test stimulus is increased above its unconditioned threshold value. Early in this period the threshold may be raised several times. With increasing stimulus interval the threshold falls steeply at first and then more slowly along a smooth curve which ends asymptotically. — Subthreshold stimulation at one spot has not been found to influence excitability at other spots within the receptive field nor has simultaneous subthreshold stimulation at two spots been found to summate and produce an action potential in the dorsal root fibre.

The excitability changes found are consistent with the observations made by CATTELL and HOAGLAND (1931) and by TOWER (1940), *viz.* that impulse activity elicited in one part of a receptive field depresses the activity initiated in another part of the field. This interaction is obviously exerted as a mutual inhibition between the receptors of a unit. It is assumed that the excitability changes found, in addition to the characteristics of the stimulus itself, will influence the frequency pattern of the discharge during natural stimulation.

Cattell, McK. and H. Hoagland, J. Physiol. 1931. 72. 392.
Tower, S. S., J. Neurophysiol. 1940. 3. 486.

Linderholm, H. (Department of Clinical Physiology, Karolinska Sjukhuset, Stockholm, Sweden): MAXIMAL PULMONARY DIFFUSING CAPACITY AND PHYSICAL WORKING CAPACITY.

The maximal physical working capacity, estimated from work in »steady state», *e.g.*, on a bicycle ergometer, is usually

limited by the maximal cardiac output. Under certain circumstances, and particularly when the maximal diffusing capacity of the lungs for oxygen is small, the diffusion processes may confine the ability of the lungs to take up oxygen. This — and not the maximal cardiac output — may then limit the physical working capacity. A relation was established between the physical working capacity and the pulmonary diffusing capacity which makes a differentiation possible between these two possibilities.

Lindgren, P. (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): AN IMPROVED METHOD FOR DROP RECORDING OF ARTERIAL BLOOD FLOW.

In 1954 LINDGREN and UVNÄS described a method for measuring venous and arterial blood flow in a closed system using a photoelectric drop recorder. However, this method, originally devised for measuring venous outflow, has some disadvantages when used for arterial recording. The most serious of these is the »Windkessel« effect exerted by the air enclosed in the drop chamber. The systolic pulses have a pronounced effect on the release of the individual drops, so that they fall at somewhat irregular intervals, which gives a step-like character to the curve. Furthermore there will be compression or expansion of the air volume when the blood pressure changes — in some types of experiment these changes may be 50—100 mm Hg. In such cases there will be a transient measuring error amounting to several drops.

Attempts have been made to correct these faults by means of a micro-modification (FOLKOW, personal communication). This procedure reduces the measuring error to only a few drops but does not eliminate the irregularity of the drop intervals.

In order to eliminate the disadvantages of the original method the following modification has now been made. The drops are allowed to fall through an incompressible liquid in

place of air. Silicon DC 200/0.65 cs, sp.gr. 0.75, a liquid not soluble in water and quite inert against blood, is suitable for this purpose. This modified method has been used for measuring the flow in the femoral artery of cats and dogs, and in the internal carotid artery of dogs and rabbits, and its main advantages are as follows:

1. Less influence of the pulse wave on the release of the drops. The drop intervals are almost as regular as in recording venous flow.

2. No measuring errors during rapid and extreme variations of the blood pressure.

3. No light obstructing »spits» of blood on the walls of the drop chamber.

4. The large drops, 7—8 per ml, (compared with 17—18 per ml when the drops fall in air from the same orifice), permit recording of higher blood flows; 30 ml per minute have been recorded without difficulties.

Lindgren, P. and B. Uvnäs, Acta Physiol. Scand. 1954. *32*. 259.

Lund, A. (Ferrosan Ltd., Copenhagen, Denmark): THE METABOLISM OF ADRENALINE IN THE PERFUSED RABBIT LIVER.

Adrenaline is rapidly inactivated in the isolated, perfused rabbit liver. On alcoholic extraction of the perfusion blood and counter-current distribution, the following substances were isolated: free and bound adrenaline (presumably the glucuronide), the deamination product dihydroxymandelic acid, and one or more lipoid soluble substances of unknown character. The total amount of degradation products found corresponds to approximately half of the amount of adrenaline originally present. The other half is believed to be degraded to such an extent that the catechol character is lost.

*Lund, A. (Ferrosan Ltd., Copenhagen, Denmark): ABSORPTION AND EXCRETION OF ORALLY ACTIVE MERCURIAL DIURETICS.

The absorption and the excretion of two Hg-diuretics, Oradon (3-hydroxymercury-2-methoxy-1-succinimidopropane, theophylline) and Chlormerodrin (3-chloromercury-2-methoxy-1-ureidopropane) have been investigated in rats, rabbits and pigs. The two compounds were synthetized with radioactive mercury (Hg^{203}), and the investigations were performed as isotopic tracer studies. Absorption and elimination of these Hg-diuretics in rodents differ much from the corresponding processes in pigs and humans.

Rodents. When administered *parenterally* about half of the amount of Hg-diuretic is excreted through the kidneys, and the other half with the faeces. 6 hours after the injection as much as 50 % of the administered amount is accumulated in the kidneys. 24 hours later the major part has been excreted in the urine, but about 5 % remains bound in the kidneys for weeks.

On *oral* administration only 15 % of Oradon and 5 % of Chlormerodrin is absorbed from the gastro-intestinal tract, about 80 % of the dose being excreted with the faeces. Significant amounts of Hg (3—4 %) are bound in the kidneys.

In chronic toxicity experiments, where Oradon was given daily for 3 months orally to rats, a steadily increasing amount of Hg accumulated in the kidneys. After 10—20 days' medication a certain level of Hg in the kidneys was reached (400 μg Hg/g of tissue). Further administration of the diuretic did not increase the Hg level. This was reduced very slowly after withdrawal of the diuretic. Dimercaprol caused liberation and excretion of the Hg bound in the kidneys. Histologically no signs of damage to the kidneys could be found except mild, reversible changes, which could not interfere with the kidney function.

Pigs absorbed 50 % of an *orally* administered amount of Oradon (chlormerodrin 25 %), while the other half was excreted with the faeces. All of the absorbed Hg is excreted with the

* Paper read at the pharmacological meeting August 30th.

urine, and less than 1 % is bound in the kidneys. Chronic toxicity experiments in pigs given Oradon orally daily for one month showed that Hg was bound in the kidneys to a small extent only (50 μg Hg/g of tissue). These results seem to correspond to those found for humans (BONDRUP and HVIDBERG 1957), in whom 50 % of an amount of Oradon administered orally is excreted in the urine.

Bondrup, K. and E. Hvidberg, Scand. J. Clin. Lab. Invest. 1957. 9. 62.

Lundin, S. J. (Research Institute of National Defence I, Sundbyberg, Sweden): OCCURRENCE AND LOCALIZATION OF ACETYLCHOLINESTERASE (AcChE) IN LEBISTES RETICULATUS AND CARASSIUS AURATUS.

It has been shown that the muscle tissue of *Lebistes reticulatus*, guppy, and *Carassius auratus*, gold fish, has an unexpectedly large cholinesterase activity. The activity corresponds to a hydrolysis of about 20 mg acetylcholine/0.1 g muscle× hour. The corresponding values for the electric organ tissue of the electric eel (*Electrophorus*), which has the highest known AcChE activity of any tissues, is 400—500 mg and for mammalian muscles about 1 mg (PROSSER 1950).

When the muscles of the guppy and the gold fish are examined for the presence of cholinesterases using KOELLE's (1951) histochemical method, as modified by HOLMSTEDT (1957), it was found that the AcChE is localized in the connective tissue between the muscle bundles. So far no end-plates have been demonstrated.

The implications of these findings regarding the function of the AcChE will be discussed.

Holmstedt, B., Acta Physiol. Scand. 1957, in press.
Koelle, G. B., J. Pharmacol. & Exper. Therap. 1951. *103*. 153.
Prosser, C. L. (Ed.), Comparative Animal Physiology 1950. 609.

Lundquist, F. and H. Wolthers (Institute of Forensic Medicine, University of Copenhagen, Denmark): THE KINETICS OF ALCOHOL ELIMINATION IN MAN.

Experiments were performed on 10 normal fasting subjects

who were given approximately 0.5 g alcohol per kg bodyweight. Two hours were allowed for absorption of the alcohol, after which venous blood samples were withdrawn at intervals of 30 min. Alcohol was determined in serum by means of modifications of the usual alcohol dehydrogenase method which permits analyses to be made at very small concentrations with an accuracy of 0.01 mg per 100 ml serum.

The curve relating serum alcohol concentration to time was found to agree very well with the theoretical curve for a process governed by an enzymic reaction with a Michaelis constant (K_m) of 1.5—2.0 mM. A simple graphical method was employed for the determination of K_m and the maximal velocity. Measurements of K_m *in vitro* for liver alcohol dehydrogenase at body temperature and in a medium of approximate physiological ionic composition gave values in the range 1.5—1.8 mM. This is considered in agreement with the theory that the rate limiting enzyme in alcohol metabolism is alcohol dehydrogenase.

It may be a clinically useful feature in this method that the maximal velocity, *i. e.* the capacity of the liver to burn alcohol, may be determined accurately at low levels of alcohol in the blood (30—40 mg/100 ml).

It should be possible to determine the K_m for many other elimination processes by means of a similar technique involving accurate determination of the disappearance curve. The interpretation of this kind of experiments and possible sources of error will be discussed.

Lybeck, H. (Medical Clinic IV, Maria Hospital, University of Helsinki, Finland): THE INFLUENCE OF HEAT ON THE ABILITY OF THE SERUM PROTEIN TO TRANSPORT RADIOACTIVE THYROXINE AND TRIIODOTHYRONINE.

Recent findings indicate that the transportation in the blood of small physiological amounts of thyroxine and triiodothyronine, irrespective of whether they are of endogenous

or exogenous origin, is due to serum protein molecules which in electrophoresis migrate to the same positions as the alpha globulins.

This alpha globulin component with a specific binding mechanism for iodothyronines apparently possesses characteristics similar to the $alpha_2$ glycoproteins. These proteins are characterized by relative resistance to denaturation. It would therefore be expected that during filter paper electrophoresis of heated serum proteins, this group of not easily coagulable mucoproteins would move on the paper strip, leaving the other coagulated fractions behind on the starting line.

In vitro experiments with guinea-pig sera heated to 40, 50, 60, 70 and 80° C and then submitted to electrophoresis for 8 hrs, showed that where the serum was heated to 70 and 80° C it was no longer possible to differentiate the bulk of the proteins from each other. There was, however, a group of protein molecules that appeared not to be influenced by heating to 80° C. These protein molecules migrated and formed a distinct group in the same position on the paper strip as the $alpha_2$ globulin molecules, while at 80° C, for instance, practically all the other serum proteins remained coagulated on the starting line. In spite of the treatment in extremely high temperatures these uncoagulated serum protein molecules had not lost their ability to bind and transport thyroxine or triiodothyronine. It was possible to demonstrate this by a slight modification of the technique.

When submitted to filter paper electrophoresis neither thyroxine nor triiodothyronine migrates appreciably on the paper strip during electrophoresis. In these experiments freshly prepared (LYBECK 1954) labelled thyroxine and triiodothyronine were used. The labelled compounds were *not* added to the sera, but placed in small amounts on a spot ahead of the serum (1½ cm beyond the starting line) before the run. The experiments were divided into two parts: *A* where the labelled iodothyronines were placed on a *soaked* paper strip; *B* where the labelled substances were permitted to become firmly attached to the paper fibres by drying. The results of the 8 hr runs of *A* demonstrated that the affinity of the uncoagulated

proteins for labelled thyroxine and triiodothyronine respectively had not been impaired by the heat treatment. During electrophoresis these proteins transported all the radioactive substance from the spot area into the alpha$_2$ position on the paper strip. Likewise in *B*, where the radioactive thyroxine or triiodothyronine was allowed to become attached to the fibres on drying, the uncoagulated protein molecules transported most of the labelled substances from the spot area. By using this »dry spot» method it was also possible to demonstrate that preheating of sera increases the capacity of the serum protein molecules to take up thyroxine and triiodothyronine.

Lybeck, H., Acta Physiol. Scand. 1954. *31*. suppl. 114. 39.

Lybeck, H. (Medical Clinic IV, Maria Hospital, University of Helsinki, Finland): »SHORT TIME» FILTER PAPER ELECTROPHORESIS, A CONVENIENT MICROMETHOD FOR SEPARATING FREE I^{131} FROM PROTEIN-BOUND I^{131} IN SERUM.

In vitro experiments in which (*a*) carrier-free I^{131} (as iodide) or (*b*) labelled thyroxine or triiodothyronine was added to guinea-pig serum and was then submitted to »short time» filter paper electrophoresis (1½ hrs) demonstrated that:

in (*a*) the carrier-free I^{131} moved more rapidly than the serum proteins and that at the end of the run it was detectable on the paper strip in an area beyond the serum protein front. In the serum protein area no appreciable radioactivity was found, not even after incubation of the serum and the I^{131} at 37° C for 24 hours;

in (*b*) the labelled thyroid hormones were attached to the serum proteins, *i. e.* all the radioactivity was detected in the protein area and none in the area beyond the serum protein front where the free I^{131} had been found (LYBECK, in press). These results prompted the use of this »short time» electrophoresis method for *in vivo* studies on I^{131} turnover in the blood and to express the rate of release of I^{131}-containing products from the thyroid.

Thirteen guinea-pigs served as experimental animals. The carrier-free I^{131} was administered and the blood samples were taken at suitable time intervals, by heart puncture. The experiments were divided into two groups: (*i*) in which only a small amount of I^{131}, and (*ii*) in which massive doses of I^{131} were administered. In (*i*) it would be expected that the I^{131}-containing substance bound to the serum proteins would be endogenous radioactive thyroxine, in (*ii*) not only radioactive thyroxine but also radioactive breakdown products released by the thyroid after radiation injury. The results of the »short time» filter paper electrophoreses showed that it was possible to separate free I^{131} from protein-bound I^{131} in the serum. In (*i*) the rate of uptake of the free I^{131} and release of radioactive hormone into the blood stream by the thyroid gland could be followed. In (*ii*), where huge amounts of I^{131} were administered, »short time» electrophoresis permitted the outflow of radioactive breakdown products and I^{131} from the thyroid gland, due to the heavy radiation, to be followed closely. It appears that »short time» filter paper electrophoresis offers a convenient micro-method for separating the protein-bound I^{131} from the free I^{131} in the serum and that it can be used for studies (with sufficiently sensitive radioactivity detectors) on the I^{131} turnover in the blood, that is, to express the rate of release of hormonal I^{131} into the blood stream by the thyroid gland.

Lybeck, H., Acta Med. Scandinav. In press.

Næss, K. (Institute of Pharmacology, University of Oslo, Norway): INHIBITION OF TETANIC CONTRACTIONS PRODUCED BY INHIBITORS OF CHOLINESTERASE.

Niemi, M. (Institute of Anatomy, University of Helsinki, Finland): A METHOD FOR QUANTITATIVE DETERMINATION OF CORPUSCULAR HEMOGLOBIN.

In 1952 ORNSTEIN proposed a new photographic method for quantitative estimation of Feulgen-positive material in in-

dividual nuclei. The main idea of his method is that, instead of integrating the blackening of the photographic image of a nucleus by scanning densitometry, the image is cut out of the enlarged positive print and the silver content of this piece is chemically determined. Using the same principle, the present writer has developed a photographic photometric method for the determination of hemoglobin in individual red blood cells.

Thin blood smears are fixed, mounted in a medium matching the refractive index of the red cells and photographed unstained. In the photomicrographic assembly a rotating sector is placed below the film holder. The steps in this sector wedge correspond to densities of 0.05, 0.1, 0.15, 0.2, 0.25, 0.3 and 0.4. The densities of red cells were found to lie within this range. The exposure is chosen so as to make the density wedge fall in the linear part of the characteristic curve of the photographic emulsion. Latent images are then developed, fixed, washed and dried under strictly standardized conditions. Positive contact prints are now made on the same film material. Again only the linear part of gamma-curve is used. Using a punch plier the images of individual erythrocytes are cut out and the silver content of these film pieces is determined chemically. The integrated density of each individual erythrocyte is obtained with the aid of the density wedge produced on each print by the rotating sector.

The all-over standard deviation of a single determination by the described method was found to be about 6 per cent. The distribution of corpuscular hemoglobin in healthy persons and in some anaemias are under investigation and some results obtained are briefly discussed.

Ornstein, L., Lab. Invest. 1952. *1*. 250.

Nisell, O. (Serafimerlasarettet, Department of Medicine, Stockholm, Sweden): THE MECHANICAL IMPEDANCE OF THE LUNGS AND AIRWAYS.

If it is assumed that the pattern of breathing is sine wave formed, that the effect of inertia on respiration is negligible

and that the resistance and compliance are constant during a breath, the mechanical impedance of the lungs and airways can be calculated in analogy to the impedance of an electric alternating current circuit as

$$\frac{\text{pleural pressure variation}}{2\ (\text{maximal flow})} = \sqrt{(\text{resistance})^2 + \frac{(\text{time of cycle})^2}{4\,\pi^2\ (\text{compliance})^2}}$$

The pleural respiratory pressure variations are obtained from an esophageal balloon. The air flow, the resistance and the compliance are determined from time marked esophageal pressure tidal volume loops. The impedance values were calculated according to the left and the right side of the equation above. For instance, in one subject the resistance was 2.4 cm H_2O/l/sec at mean flow, the compliance 0.19 l/cm H_2O and the impedance calculated according to the left side of the equation 3.3 cm H_2O/l/sec and according to the right side 3.4 cm H_2O/l/sec. In another subject who had bronchial asthma the resistance was 14 cm H_2O/l/sec, the compliance 0.05 l/cm H_2O and the impedance 19 and 17 cm H_2O/l/sec according to the left and right sides of the equation respectively. The impedance figure appears to offer a pertinent value for the clinical evaluation of breathlessness because it expresses the combined hindering effect on breathing of the respiratory resistance and the lung compliance.

Olsson, S. (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): SECRETORY RESPONSES TO HISTAMINE AND GASTRIN IN ANAESTHETISED AND NONANAESTHETISED GASTRIC FISTULA CATS.

A method has been devised to test the effects of stimulating and inhibitory agents on gastric secretion in nonanaesthetised cats, provided with gastric fistulas. As stimuli we have used histamine and extracts from the pyloric mucosa of cat prepared according to KOMAROV (1938) and UVNÄS (1942). Both substances were given i. v. during 15 minute periods, repeated hourly or continuously during 3—4 hours.

For *nonanaesthetised* cats, infusions of histamine in doses

of 0.03 mg/kg/15 min could be repeated every hour at least six times with almost uniform responses, provided that the output of HCl does not exceed 0.6 mEq/hour. Similar consistent responses could be obtained with pyloric extracts. We have also found that the secretory responses of any animal will remain constant over several months. No signs of anaphylactic reactions to pyloric extracts occurred. The blood pressure, recorded in art. lienalis of splenectomised, gastric fistula cats, was not influenced either by histamine or pyloric extracts in the doses employed.

When repeating the experiments on *anaesthetised* cats (0.05 g chloralose and 0.5 g urethane per kg bodyweight i. v.) we found that to get an equivalent secretory response to histamine we had to give 3—5 times larger doses than to nonanaesthetised cats. These animals showed a pronounced tachyphylactic reaction; the second dose gave only a small response. The minute third response could not be increased even with double the first dose. The secretory responses to histamine showed a great variation from cat to cat. The blood pressure fell instantly from 110 to 60 mm Hg and the recovery was uncertain. With pyloric extracts, we had to use about 8 times the doses given to nonanaesthetised cats. The dose could be repeated hourly but the secretory responses varied greatly. Besides, it is difficult to get a predictable response because of the great variation between animals. The administration of pyloric extracts did not affect the blood pressure.

Further observations made will be discussed.

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Oscarsson, O. (Institute of Physiology, University of Lund, Sweden): FURTHER OBSERVATIONS ON ASCENDING SPINAL TRACTS ACTIVATED FROM MUSCLE, JOINT, AND SKIN NERVES.

Previously the functional organization of the dorsal and ventral spino-cerebellar tracts (DSCT and VSCT) has been

analysed by the aid of mass discharge recording from dissected spinal halves (except dorsal columns) and micro-electrode recording from fibres in the lateral funiculi (HOLMQVIST *et al.* 1956, LAPORTE *et al.* 1956 a, b, c, LUNDBERG *et al.* 1956 and OSCARSSON 1956). These methods have now been used for a further investigation of the tracts responsible for the other components of the compound mass discharge recordable from the dissected spinal halves on muscle, joint, and skin nerve stimulation. It has been shown that these discharges are mainly due to activity in five well-defined groups of ascending fibres (including the two groups constituting the DSCT and VSCT). Except VSCT fibres, the ventrolateral funiculus contains fibres which are characterized by receiving excitatory action from ipsilateral and contralateral high threshold muscle and joint nerve afferents and high and low threshold skin nerve afferents. The convergence of excitatory action is very extensive and most units belonging to this group could be discharged from all the dissected ipsilateral and contralateral muscle, joint, and skin nerves. Supramaximal stimulation usually evokes a train of impulses in these fibres. The conduction velocity of the fastest fibres amounts to about 100 m/sec. The dorso-lateral funiculus contains, except DSCT fibres, two other groups of ascending fibres (*cf.* HOLMQVIST *et al.* 1956). One of these consists of fibres similar to those just described but receiving excitatory action only from the ipsilateral nerves. The other group consists of fibres solely activated from ipsilateral skin nerve afferents.

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Östling, G. (Pharmacological Laboratory, OY Medica AB, Helsinki, Finland): SIMULTANEOUS INTESTINAL ABSORPTION OF SOLUTE AND SOLVENT.

If a radioactive phosphate solution (*I*) with a lower specific weight than blood is infused slowly into a vein and the blood is tapped from the vein a short distance away and allowed to flow via a cannula into a test tube, the radioactive phosphate does not spread evenly through the blood in the tube but rises to the surface (ÖSTLING 1952). If the same test is made with 50 % glucose solution mixed with a small amount of radioactive phosphate solution (*II*), both the radioactive phosphate and the glucose settle to the bottom. Solution *II* has a greater specific weight than blood. These examples illustrate the phenomenon that a solution of lower specific weight than blood floats when infused in the venous system, while a solution of a higher specific weight settles.

For the intestinal absorption experiments a loop of the small intestine is exposed after laparatomy on rabbits. Both the exposed intestine and its arteries are left intact. A cannula is introduced into the mesenteric vein which collects the blood from the intestinal section in question. 5 ml of the test solution is injected into the intestinal lumen. All the blood that flows from the mesenteric veins is collected in small test tubes immediately after the injection. 4—8 tubes of blood in unbroken succession are taken in each test. In the test with solution *I* the radioactive phosphate floats, and with solution *II* both the glucose and the radioactive phosphate settle to the bottom.

The tests prove that the solutions of lighter or heavier specific weight, after absorption via the intestinal epithelium, are also in the mesenteric vein lighter or heavier, respectively, than blood as regards specific weight. This would appear to indicate that both the solute and the solvent are absorbed simultaneously. A condition for this is the existence of direct connections between the intestinal lumen and intestinal capillaries. Hippocrates and Galen were of the opinion that the absorption takes place via openings in the veins. COLLANDER (1924) asserted that permeation via cell membranes

occurs partly through pores (Lipoid-pore theory). The above findings concur with the part of the fluid circuit hypothesis (INGRAHAM and VISSCHER 1938) which presupposes a stream of fluid from the intestinal lumen to portal blood. They also concur with the findings of FULLERTON and PARSONS (1956) that the rate of absorption of sugars from solutions is directly proportional to the water absorption rate.

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Pascoe, J. E. (Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden): THE RESPONSES OF ANTERIOR HORN CELLS TO APPLIED CURRENTS.

GRANIT, HENATSCH and STEG (1956) have classified the alpha motor cells supplying the gastrocnemius-soleus muscle group as either phasic or tonic according to their reactions to muscle stretch. This raises the question whether the two types of response are caused by different properties of the respective cell membranes. In an attempt to answer this question a study has been made of the responses of anterior horn cells to direct electrical stimulation. This report is concerned with the preliminary results, mainly from unidentified anterior horn cells.

The cells were originally stimulated by electrotonic spread along the ventral root but this was insufficiently selective. The method of fixation introduced by GRANIT, PHILLIPS, SKOGLUND and STEG (1957) has allowed the introduction of microelectrodes into anterior horn cells of decerebrate, reflexly active cats, and with the electrode in one arm of a bridge it has been possible to stimulate and record simultaneously with the same electrode. The method unfortunately does not allow the measurement of the change of the resting potential during stimulation.

The results with long current pulses confirm the findings of BARRON and MATTHEWS (1938). Depolarizing currents caused most of the studied cells to fire repetitively and for long periods with little or no sign of accommodation. It was possible with low current intensities to cause the cells to fire once only at the make, but a slight increase of current led to repetitive discharge. Anodal currents slowed or, if sufficiently strong, stopped cells that were already discharging repetitively.

Cells identified as tonic by the criteria of GRANIT *et al.* (1956) could be made to fire repetitively by cathodal polarization. It has not been possible to identify any phasic cells with certainty as yet since the quick stretch necessary to excite them dislodges the electrode.

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Pekkarinen, A. (Institute of Pharmacology, University of Turku, Finland): ON THE ADRENOCORTICAL RESERVE AND THE EXCRETION OF 17-HYDROXYCORTICOSTEROIDS, 17-KETOSTEROIDS, NORADRENALINE AND ADRENALINE IN MIDDLE AGED AND ELDERLY PATIENTS AFTER SURGICAL OPERATIONS.

Adrenocortical function has been studied in 225 patients by determining the total 17-hydroxycorticosteroid content in the urine after daily intramuscular injection of 80 units depot ACTH. In a group of patients with rheumatoid arthritis, uterus carcinoma, diabetes mellitus and neurasthenia the average quantity of total 17-hydroxycorticosteroids excreted during the first ACTH day was normal, 14.5 mg (171 cases). On the second ACTH day the average quantity excreted was twice as high, *i. e.* 28.0 mg (123 cases). On the third ACTH day the

quantity excreted reached a maximum, 38.0 mg (27 cases), and was higher in men than in women. The average excretion of total 17-hydroxycorticosteroids after ACTH administration was higher during the first day in patients with chronic tuberculosis and acne, 24.3 mg (37 cases) and 28.4 mg (9 cases), and higher in patients with acne during the second day, 54.0 mg; it was lower in patients with endogenic depression during the first and second ACTH days.

In major surgical operations on 102 patients (55 males and 47 females, average age 40 years) and 52 elderly patients (average age 63.5 years) the average quantity of total 17-hydroxycorticosteroids excreted during the 24 hours preceding operation was 5.0 mg (HALME, PEKKARINEN and TURUNEN 1957; PEKKARINEN, VIIKARI and TURUNEN 1957). During the first two postoperative days the excretion in males increased to 28.0 and 28.6 mg and in females to 16.3 and 15.1 mg. In the old age group it increased during the first two days to 16.0 and 21.7 mg. Males usually showed stronger reactions than females after operation. The increased excretion of 17-ketosteroids was small in comparison with the increased amount of total 17-hydroxycorticosteroids excreted.

The daily average quantity of noradrenaline excreted before operation was 26.4 μg in males and 21.7 μg in females. On the first and second day after operation this increased in males to 64.3 and 71.2 μg and in females to 34.6 and 38.8 μg. The average excretion of adrenaline before operation was 4.8 μg in males and 3.7 μg in females. After operation it increased for two days in males to 14.4 and 17.1 μg and in females to 9.9 and 9.0 μg. The quantities of noradrenaline and adrenaline excreted were higher in males than in females. The increased excretion of total 17-hydroxycorticosteroids, noradrenaline and adrenaline after operation indicates that a functional correlation seems to exist between these substances.

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Pulkkinen, M. (Institute of Physiology, University of Turku, Finland): **THE ARYLSULPHATASE CONTENT OF THE HUMAN EMBRYONIC TISSUE AND PLACENTA BY USING p-NITROPHENYLSULPHATE AS SUBSTRATE.**

Studies have been made on the arylsulphatase content of human embryonic tissue by using the method introduced by HUGGINS and SMITH (1947). In this method p-nitrophenylsulphate is used as substrate.

The following homogenate concentrations were found to be optimal: liver 0.2, intestine, kidney and placenta 1, liver and pancreas 3, heart, spleen and brain 10 per cent. The results are not fully comparable due to the difference in the protein inhibition of various tissues. The pH optimum for the various tissues was found to be different when measured in sodium acetate-acetic acid buffer: liver, pancreas and intestine 7.3, lung and kidney 7.1, genital organs (6 months female) 6.8. The substrate concentration optimum was determined for liver and kidney; it was found to be 0.008 M which is the same as DODGSON *et al.* (1956) have found by using human liver-acetone powder.

The following procedure was used: 1.5 ml of the buffer solution and 0.5 ml of the homogenate were first incubated for 3 minutes. After this 0.5 ml of the substrate solution was added. The temperature in the water bath was kept at 37° C. The optimal temperature for the hydrolysis has been stated to be 40 and 50° C for rat liver, but RUTENBERG and SELIGMAN (1956) claim that the function curve for time is linear only at 37° C. This was found to be true also in our experimental conditions. After the incubation the volume was increased with 2.5 ml of water and the reaction stopped with 0.5 ml of 10 per cent $ZnSO_4$. The protein-precipitation was carried out in alkaline pH since it absorbs chromogens when precipitated in acid environment. $ZnSO_4$—NaOH has been used. SOMOGUI (1945) recommends these reagents in the following ratio: 0.3 N NaOH and 5 per cent $ZnSO_4$ in equal parts. The formed complex absorbs, however, all of the liberated p-nitrophenol. Using 0.5 ml of 10 per cent $ZnSO_4$ and 0.8 ml 0.5 N NaOH, as KIRK and DYRBYE (1956)

have suggested, a complete precipitation of proteins is achieved and a 100 per cent recovery if the precipitate is filtrated within 5 minutes. By allowing the solution to stand, the complex changes so that after 30 minutes or longer standing the recovery is only 30—40 per cent.

The color intensity was measured with a Beckman spectrophotometer at the wave length of 402 mμ. This optimum has been established by DODGSON *et al.* (1956) and also confirmed in our experiments.

Preliminary studies have revealed the following arylsulphatase concentrations in human embryos and placentas; results calculated in micrograms of liberated p-nitrophenol per hour and 1 gram of tissue wet weight: *liver* 7 000—15 000, *intestine* 2 000—8 000, *stomach* 100—300, *pancreas* 3 500, *kidney* 150—1 500, *adrenals* 25—125, *lung* 50—500, *thyroid* 25—60, *brain* 30—300, *testis* 90. In the placenta the foetal side had slightly more enzyme concentrations, the range being 1 200—4 500.

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Räihä, N. (Department of Physiology, Institute of Occupational Health, Helsinki, Finland):

OBSERVATIONS ON THE FETAL UPTAKE OF ASCORBIC ACID.

The distribution of l-ascorbic acid (AA), dehydroascorbic-acid (DHA) and total ascorbic acid (TAA) has been studied in the fetal and maternal blood of man and guinea pig. The plasma TAA values in human umbilical cord are generally about twice as high as those of the maternal plasma. In the guinea pig the fetal plasma contains somewhat less TAA than the maternal plasma. The AA concentration in human cord blood is considerably higher than the values for DHA, in the maternal blood AA and DHA are distributed more equally. In the guinea pig and in man DHA passes rapidly into the erythrocytes,

whereas the passage of AA into the erythrocytes is slow. The vitamin C content of erythrocytes was determined only as TAA due to the rapid conversion of AA to DHA by hemolysed red cells.

A slow increase of TAA in the fetal plasma of both man and guinea pig can be shown during infusion and after injection of AA into the maternal circulation. Studies on the passage of DHA from mother to fetus are not completed.

After maternal oral intake of AA during a period of some days the TAA values in cord blood are about twice as high as in the cases where no AA has been added.

In the cases where AA has been administered to the mother the amniotic fluid shows values of TAA which are considerably higher than the corresponding values of cord blood.

Rosenfalck, A. and P. Rosenfalck (Institute of Neurophysiology, University of Copenhagen, Denmark): BIREFRINGENCE OF ISOLATED MUSCLE FIBRES DURING ISOMETRIC CONTRACTION.

Small bundles of striated frog muscle fibres (2—10) were placed in a slit which limited the light passing through the fibres. The slit was illuminated homogeneously from a tungsten lamp through interference filters. Birefringence changes were determined photoelectrically measuring the monochromatic light transmitted through fibres placed between crossed and parallel polaroid plates.

For comparison, the birefringence at rest was determined by means of a Babinet compensator. It was thereby observed that the phase difference varied considerably across the larger fibre bundles. Therefore preparations containing only a few fibres were used.

With the muscle fibres placed at an angle of 45 degrees to the polarising direction of the polariser, the light transmitted through the fibres and the analyser is maximum or minimum according to whether the polarising direction of the analyser

is perpendicular or parallel to that of the polariser. The intensities in the two directions are:

$$I_{=} = I_o \left[1 + \cos \frac{2\pi}{\lambda} d \ (n_x - n_y)\right]$$

$$I_{\perp} = I_o \left[1 - \cos \frac{2\pi}{\lambda} d \ (n_x - n_y)\right]$$

where λ is the wavelength of the light, d the thickness of the fibre bundle, n_x and n_y the refractive indices in the longitudinal and transverse direction of the fibres, and I_o a proportionality factor. Changes in the birefringence $(n_x - n_y)$ are therefore accompanied by changes in $I_{=}$ and $I_{\perp}$, the changes being identical in size but of opposite direction.

When using monochromatic light of different wavelengths good agreement was obtained with the theoretical expectations.

During isometric twitches of slightly stretched frog muscle fibres changes in the intensity of light transmitted amounted to up to 50 per cent. The changes in intensity due to variations in absorption, diffraction or thickness of the fibres were controlled in each experiment; experiments were only considered when they amounted to less than 5 per cent. The changes in light transmitted corresponded to a decrease in birefringence of up to 20 per cent. The decrease in birefringence reached its maximum within about 10 msec (20° C), the total duration of the change being 60—150 msec.

Rosenfalck, P. (Institute of Neurophysiology, University of Copenhagen, Denmark): VOLUME CONDUCTED ACTION POTENTIALS AND THEIR CORRELATION TO THE INTRACELLULAR POTENTIALS.

To correlate action potentials with the current sources from which they arise, knowledge is required of the spread of the action currents from the individual cell. This spread is determined by (*1*) the time course of the depolarization and repolarization of the surface membrane, (*2*) the extent of the depolarized region along the current source, (*3*) the diameter of the source, and (*4*) the structure and conductivity of the

surrounding medium. In the present study the theoretical analysis of the volume conduction of nerve action potentials (LORENTE DE NÓ 1947) was generalized so as to illustrate the influence of these different factors.

The volume conducted nerve action potential was calculated from the monophasic action potential V_e recorded from the surface of the nerve when placed in an insulating medium. The volume conducted potential from a cylindrical current source depends on the second derivative of V_e, *i. e.* its curvature. This is proportional to the action current passing through the surface of the cell per unit length. On the other hand, the current also being proportional to the second derivative of the intracellularly recorded potential V_i, the volume conducted potential can be calculated from the second derivative of this potential as well. The larger the extent of the monophasic potentials (V_e and V_i) along the cell, the wider is the spread of the volume conducted action potential. The logarithm of the amplitude of this potential decreases nearly linearly with the logarithm of the distance from the axis of the cell, the slope of the curve being the same for different cells with identical shape of the monophasic potential.

In situ, inactive cells surrounding the active one act as insulators (BUCHTHAL, GULD and ROSENFALCK 1955). This causes the conductivity of the medium surrounding the active cell to be in the transverse direction only about half that along the cell. Thereby the transverse spread of the action currents is reduced by 30 per cent. Hence, the amplitude-distance relationship is steeper for cells *in situ* than for cells placed in an isotropic conductor as, *e.g.,* a bath of Ringer's solution.

Experimental findings on muscle fibres support the present results (BUCHTHAL, GULD and ROSENFALCK 1957, HÅKANSSON 1957).

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Rud, J. (Institute of Neurophysiology, University of Copenhagen, Denmark): ACTION OF LOCAL ANESTHETICS ON THE ACTION POTENTIAL OF ISOLATED, PERIPHERAL NERVE.

With the amplitude of the action potential and its conduction velocity as indicators, a number of pharmacodynamic actions of xylocaine and procaine were investigated on isolated frog nerve. The nerve was soaked in different concentrations of xylocaine- and procainehydrochloride at different pH. A given concentration of the free anesthetic base, derived from different concentrations of the anesthetic salt at different pH, gave the same reduction in the action potential amplitude. Hence, the free base is the true anesthetic factor. This result is in accordance with previous findings on the corneal reflex (TREVAN and BOOCK 1927) and nerve-muscle preparations (EHRENBERG 1948).

Different local anesthetics were compared by their minimum concentration and speed of blocking action. These data were determined in assuming that the anesthetic penetrates the nerve by diffusion. Theoretical diffusion curves were constructed of the distribution of the anesthetic base over the cross section of the nerve as a function of concentration and time. The theoretical curves fit the experimental findings of the blocking effect of the free base, and allow a determination of minimum concentrations and diffusion coefficients.

The minimum concentration for xylocaine base was 0.2 mM, its diffusion coefficient $3.1 \cdot 10^{-7}$ cm^2/sec. For procaine the minimum concentration was 0.02 mM and the diffusion coefficient $1.17—1.51 \cdot 10^{-7}$ cm^2/sec.

The recovery time of the action potential amplitude increased with the concentration of the anesthetic base and the diameter of the nerve. The recovery time was zero, at the minimum concentration. Xylocaine which had the highest minimum concentration and diffusion coefficient had the shortest recovery time.

The conduction velocity decreased in an anesthetized nerve, because of the action of subminimal concentrations. For

different local anesthetics the conduction velocity decreased to the same extent, if the anesthetic base concentrations were expressed in units of their minimum concentrations.

The delay in the blocking time (1.4 times) of the intact nerve as compared with the desheathed nerve, could be accounted for by gradual diffusion of the anesthetic through the sheath.

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Rushton, W. A. H. (Physiological Laboratory, University of Cambridge, England): THE LACK OF A RED-SENSITIVE PIGMENT IN THE PROTANOPE.

Protanopia is the kind of red-green colour blindness where the subject is insensitive to the red end of the spectrum. Ever since Helmholtz this has been attributed to loss of the »red mechanism« but it has not been known whether the defect lay in the pigment, the specific nerves or in some discriminating mechanism of the brain.

Now physical analysis of the light reflected from the eye by an ophthalmoscopic arrangement (RUSHTON and CAMPBELL 1954) permits the measurement of rhodopsin when the periphery of the normal human eye is examined. When the light thus analysed comes exclusively from the fovea, it is cone pigments that are measured (RUSHTON 1957). The fovea is blue-blind (KÖNIG 1894, WILLMER 1944) and no blue-sensitive pigment has been detected but the normal fovea contains two other photo-labile pigments, one absorbing maximally at 540 mμ and one at 590 mμ. What is the condition upon the fovea of the protanope? It is found that only the 540 mμ pigment is present as may be seen from the following observations.

(*a*) No bleaching follows exposure to a deep red light which in the normal eye bleaches the red-sensitive pigment.

(*b*) The spectral change of the pigment is the same upon bleaching with orange light or with green. Thus only one visual pigment is being measured, and its maximum is found to be at 540 mμ.

(c) If only one pigment underlies the protanope's sensation of brightness, then his luminosity curve ought to coincide with the absorption curve of the pigment, as has long been known to be the case with twilight visibility and the absorption spectrum of rhodopsin. In the protanope the agreement is good.

These objective measurements, then, confirm what has long been suspected from psycho-physics, that protanopes lack red sensitivity because they lack the red-sensitive cone pigment. The »red» cones, however, do not stand empty, for there is considerably more green-sensitive pigment in the protanope than in the normal. Evidently the cones which lack the pigment for red contain the pigment for green.

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Savola, P. (Institute of Physiology, University of Turku, Finland): ACTIVITY OF β-GLUCURONIDASE OF VARIOUS HUMAN TISSUES DURING THE EMBRYONAL DEVELOPMENT.

β-glucuronidase, the enzyme belonging to the carbohydrase group, has received a considerable amount of experimental interest during the last ten years. β-glucuronidase has been chemically isolated and its chemical, physical and enzymatic characteristics have been well explored. It is widely spread in various tissues and organs, and several theories concerning its functions in animal organism have been presented.

FISHMAN (1940) has assumed, that β-glucuronidase is involved in the glucuronide synthesis. He postulates also that a »metabolic conjugation» takes place in the organism between β-glucuronidase and the estrogenic hormones (FISHMAN 1947). KERR and coworkers (1947) have assumed that β-glucuronidase is closely connected to tissue proliferation

Several reports on the effect of pregnancy on the β-glucuronidase content in the organism are available. BERNARD and ODELL (1950) have found that pregnancy causes an increased β-glucuronidase activity in rat liver and blood serum. This increased activity can be prolonged after the parturition by giving the animals estrogens (FISHMAN 1947; ODELL and McDONALD 1948). PANATTONI (1954 a, b) has studied the renal β-glucuronidase activity during intra-uterine development by bio- and histochemical means.

In the present preliminary work the author has studied the β-glucuronidase activity of several embryonal tissues during various phases of intra-uterine development. The tissues were weighed and homogenised in a Potter-Elvehjem glass homogeniser. The analyses were made by using 0.1 ml of 1—3 per cent aqueous homogenate. The usual concentration is 0.5—1 per cent but owing to the high water content of embryonic tissues the concentration of our homogenates had to be increased. The β-glucuronidase activity was determined according to the TALALAY-FISHMAN-HUGGINS method (1946), applying the modification by FISHMAN, SPRINGER and BRUNETTI (1948). Simultaneously the protein nitrogen content was determined and the β-glucuronidase activity was calculated separately per 1 g tissue wet weight and per 1 mg protein nitrogen. The analyses calculated on the basis of wet weight gave the following results:

liver 1077—3125 units, *kidney* 408—1405 units, *lung* 264—375 units, *pancreas* 690—1309 units, *spleen* 970—2213 units, *adrenals* 730—1333 units, *thymus* 450—2024 units, *heart* 212—433 units, *stomach* 192—1538 units, *duodenum* 990—2014 units, *jejunum* 1416—3233 units, *ileum* 1450—4000 units, *colon* 833—2452 units.

Results based on the protein nitrogen content were as follows:

liver 48—228 units, *kidney* 53—156 units, *thyreoid* 49—130 units, *lung* 19—44 units, *pancreas* 47—77 units, *spleen* 73—88 units, *adrenals* 41—62 units, *thymus* 30—75 units, *heart* 12—30 units, *stomach* 21—55 units, *duodenum* 73—122 units, *jejunum* 100—215 units, *ileum* 94—171 units, *colon* 66—150 units.

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Schambye, P. and F. Tarding (Novo Therap. Laboratory, Copenhagen, Denmark): THE ACTION OF HYPOGLYCEMIC SULPHONYLUREAS UPON THE BLOOD SUGAR REGULATION.

The dynamic equilibrium between the glucose output from the liver and the extrahepatic utilization of glucose determines the blood sugar level. These two processes can be studied in the intact animal by introducing C^{14}-labeled glucose into the body-glucose pool, either through a single intravenous injection or a constant infusion. In the present studies, the former technique has been applied to normal and pancreatectomized dogs as well as to patients with diabetes mellitus.

The normal decrease in the labeling of the blood glucose was estimated for about 2 hours, after which 0.1 g/kg of p-tolylsulphonylbutylcarbamide (D-860) was injected intravenously. This dose produced a fall in the plasma glucose concentrations from about 110 mg % to 50 mg %, accompanied by a cessation in the constant decrease of the plasma glucose specific activity. Later, when the low blood sugar level was established, the activity again started to decrease at a nearly constant rate.

The output from the liver of unlabeled glucose is responsible for the constant dilution of the plasma glucose activity. While the peripheral utilization does not change the level *per se*, the replacement of utilized sugar represented by this output produces decrease in the specific activity. Thus the findings

described above indicate that the steep decrease in the blood sugar concentration after the injection of D-860 can be due to a blocking of the glucose output from the liver for the period in which the blood glucose specific activity remains nearly unchanged.

The action of insulin was studied in a similar manner and it is concluded that the oral hypoglycemic substances produce the decrease in the blood sugar of either normal or diabetic individuals by inhibiting the glucose output from the liver. In the case of insulin the main action is a stimulation of the peripheral utilization of glucose. However, a shortlasting decrease in the liver output can be observed when large doses (0.5—1.0 i.u./kg) are injected intravenously into normal dogs. Furthermore, it will be demonstrated how the action of the sulphonylureas is almost eliminated or delayed when the glucose output from the liver is altered by other means.

Scholander, P. F. and G. Sundnes (Institute of Zoophysiology, University of Oslo, Norway): GAS SECRETION IN FISHES LACKING »RETE MIRABILE».

Various species of Salmonides are capable of depositing nitrogen into their swimbladder against a considerable pressure gradient. We have investigated two such species, namely a deep water form of common char, *Salmo alpinus*, and the whitefish *Coregonus lavaretus*. Buoyancy tests showed that the gas was deposited at a depth of 50 m or more. The char deposits some 99 % N_2, reaching up to 9 atm. pressure. Our whitefish deposits both nitrogen and oxygen into the swimbladder, with pO_2 up to 4.5 atm. and pN_2 up to 2.5 atm. Neither species possesses a counter current multiplying system (rete mirabile) which could step up a small primary pressure effect. Therefore, if the primary pressure development of oxygen were to take place in the blood it must amount to at least 4.5 atm. The oxygen capacity in the blood is 9 vol % and can produce no more than half of that pressure at 4° C even if all oxygen were liberated. It was further found that the amount of nitrogen

which could be dissociated from air-equilibrated blood of 4° C by acid ferricyanide and vacuum was no more than corresponding to the physically dissolved nitrogen. The solubility of nitrogen in the blood at various pressures followed exactly Henry's law. It seems that neither oxygen nor nitrogen is capable of producing enough pressure in the blood to account for the tension found in the swimbladder by simple diffusion. One is here, like in deep sea fishes, forced to consider an active transport process by the epithelial cells lining the swimbladder.

***Schou, J.** (Institute of Pharmacology, University of Copenhagen, Denmark): ABSORPTION OF DRUGS FROM CONNECTIVE TISSUE, ESPECIALLY REGARDING THE ABSORPTION FROM SUBCUTANEOUS TISSUE.

Sjöstrand, T. (Karolinska Sjukhuset, Department of Clinical Physiology, Stockholm, Sweden): THE RELATIONSHIP BETWEEN THE STROKE VOLUME OF THE HEART AND THE CAPACITY OF THE VASCULAR SYSTEM.

Recent investigations on humans seem to indicate that the stroke volume of the heart is fairly constant under normal conditions. Accordingly, during exercise the stroke volume as a rule remains unchanged. This suggests that the stroke volume is regulated in such a way as to maintain a certain optimal volume and is, to a great extent, independent of the variations in the total cardiac work. It has been considered worth while to try to elucidate the factors determining this optimal value of the stroke volume.

As direct values of the stroke volume in different animals are lacking, the oxygen uptake per heartbeat (oxygen pulse) has been used as a representative value for a correlation analysis. As demonstrated earlier, there is a linear correlation between the oxygen pulse and the body weight in various

* Paper read at the pharmacological meeting August 30th.

mammals. However, the distribution of the values round the regression line has been found to correspond largely to the variation in different species as regards blood volume and to some extent also the hemoglobin concentration of the blood. Thus, a very high direct correlation occurs between the oxygen pulse, on the one hand, and the total amount of hemoglobin, on the other. This indicates that the stroke volume in mammals is adapted to the capacity of the vascular system. The same has been ascertained in a material comprising children, women and men, some of whom were physically well-trained. Direct determinations on humans have shown that the stroke volume constitutes, on an average, about 2 % of the blood volume. This regulation principle seems to be maintained also in pathological conditions, when there is no direct hindrance to an adaptation of the stroke volume.

Skou, J. C. (Institute of Physiology, University of Aarhus, Denmark): THE ENZYMIC ACTIVITY OF A MONOMOLECULAR LAYER OF ACETYLCHOLINESTERASE.

A procedure has been developed for determining the activity of enzymes spread on the surface of a solution containing the substrate.

When the enzyme has been applied to the surface, it is permitted to spread freely for a certain time and is then compressed to a fixed surface pressure. Adsorbed, not spread, protein is removed from the monolayer by stirring the water phase, and the monolayer is then moved to the surface of a clean substrate solution. The enzymic activity is then determined by measuring the breakdown of the substrate in the water phase below the monolayer.

It has been found that the activity of surface-spread acetylcholinesterase from the electric tissue of *Electrophorus* varies with the time interval between the application of the enzyme to the surface and the compression of the monolayer. It is further dependent on the surface pressure applied.

Under optimal conditions, *i. e.*, with a spreading time of 30 seconds and a surface pressure of 10 dyne/cm, the activity of surface-spread acetylcholinesterase is about 50 per cent of the activity shown by the enzyme in solution.

Söderberg, U. (Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden): THE RELATION BETWEEN THYROID CIRCULATION, UPTAKE OF IODINE AND SECRETION OF THYROID HORMONE IN CATS AND RABBITS.

Venous outflow from the thyroid gland was measured in lightly anaesthetized cats and rabbits. After having given a signal to an ordinate recorder the drops fell on a slowly running strip of filter paper and were dried and analyzed for radioiodine by a scintillation counter. Drops of arterial blood were taken in a similar way. A few times in each experiment larger samples of venous and arterial blood were taken to obtain accurate comparison between arterial and venous concentration of I^{131}. The blood taken from the animal was replaced by dextran or blood from another animal.

Uptake of iodine was studied by giving I^{131} in a single dose intravenously soon after the beginning of the experiment, and thyroid hormone secretion by giving I^{131} two to three days before the experiment.

It was found that uptake of iodine was largely proportional to blood flow through the gland. Thus the A-V difference of I^{131} could be roughly constant during considerable periods of time independent of moderate changes in blood flow. However, during severe vasoconstrictions the A-V difference fell and increased during large dilatations. These effects were less marked when the animals were breathing pure oxygen and increased in magnitude during inhalation of gas mixtures which lowered the oxygen saturation of blood or increased the carbon dioxide tension. Such procedures also influenced the uptake of iodine even when the circulation seemed to be uninfluenced. This relation between blood flow and uptake of iodine was in

principle the same independently of the method by which the changes in circulation were elicited. Vasoconstriction was produced by electrical stimulation of the cervical sympathetic trunk, by hypothalamic heating, by bleeding the animal, by nociceptive stimuli or by administration of adrenaline, noradrenaline, vasopressin or ACTH and sometimes appeared »spontaneously». Vasodilatation could be elicited by heavy doses of thyrotropic hormone, by electrical stimulation of the superior laryngeal nerve and by all procedures which released a prevailing vasoconstriction. The vasomotor effects were more pronounced in rabbits than in cats.

The secretion of thyroid hormone seems, in contrast to the uptake of iodine, to follow the secretion or administration of thyrotropic hormone, regardless of the circulation through the gland. Thus, the venous concentration of thyroid hormone increased considerably during periods of vasoconstriction and decreased during vasodilatation.

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Sperber, I. (Institute of Animal Physiology, Lantbrukshögskolan, Uppsala, Sweden): THE BILIARY EXCRETION AND CHOLERETIC EFFECT OF SOME PHENOLSULPHONEPHTHALEINS.

Phenol red and some of its halogenated derivatives have been shown to be strongly concentrated in the bile in the isolated perfused frog liver (HÖBER and TITAJEW 1929). In connection with studies of the renal secretion of phenolsulphonephthaleins (SPERBER 1954) the biliary excretion of a number of phenol red derivatives has been examined, mainly in the chicken. Most of the experiments have been performed with phenol red and brom cresol green.

One of the two bile ducts existing in the chicken has been cannulated with a polyethylene tube. After healing, the animals

usually remain in good health with little care. Continuous intravenous infusion has been used.

All the investigated sulphonephthaleins are concentrated in the bile to a considerable extent. The chicken liver shows a clearly limited transport capacity for brom cresol green and brom phenol blue. There are indications that the secretory capacity for phenol red is also limited, but in any case the transport capacity for phenol red is much higher than for brom cresol green (as is the case in the renal proximal tubule).

The secretion of phenol red is strongly decreased by simultaneous infusion of taurocholate, glycocholate or brom cresol green. The secretion of taurocholate is depressed by doses of brom cresol green which exceed the maximal transport capacity for brom cresol green.

It is concluded that taurocholates, glycocholates, bile alcohol sulphuric esters (in lower vertebrates), bilirubin-glucuronide, the phenolsulphonephthaleins (and many other aromatic organic anions) are secreted into the bile by a common mechanism which is very similar to the mechanism responsible for the secretion of, *e. g.*, hippuric acids, phenol sulphuric esters, glucuronides and phenolsulphonephthaleins in the renal proximal tubule.

Phenol red is consistently active as a choleretic and it is possible to achieve bile flows of about the same magnitude as those found during infusion of considerable amounts of taurocholate. Brom cresol green is choleretic when the basal bile flow is low and may be distinctly anticholeretic when the bile flow is high before the infusion of brom cresol green. The maximal bile flow during brom cresol green secretion is much lower than that during maximal phenol red secretion.

These findings are consistent with the hypothesis that the secretion of the above mentioned organic anions is the primary event in bile formation and that water and inorganic ions are transferred from blood to bile by the osmotic effect of the relatively large organic ions, whose passage from bile to blood is restricted.

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Sperber, I., Arch. internat. Pharmacodyn. 1954. *97*. 221.

Steg, G. (Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden). INTRAVENTRICULAR ACETYLCHOLINE INJECTIONS.

The aim of this work has been to study the plastic rigidity seen in so-called catatonic cats. FELDBERG and SHERWOOD (1954) showed that injections of acetylcholine into the lateral ventricles of cats produced a condition very like the catatonia in man.

This method of producing catatonia appeared to be of some interest, yet the results, on repetition in this laboratory, proved disappointing. In a total of 15 cats only one showed a definite plastic rigidity.

In 11 cats the left front limb was acutely deafferented, 7 under thiogenal and 4 under ether anaesthesia. Then before injecting the acetylcholine the cats were allowed to regain consciousness. In 10 of these no definite plastic rigidity appeared. It was supposed that this might have been due to the severity of the previous operation since FELDBERG and SHERWOOD worked with chronically implanted cannulae. In 4 cats therefore the cannulae were implanted during a short ethyl chloride anaesthesia and no further operations made on the animals. The skin around the wound was anaesthetized with xylocain and the animals were left to recover. Within two hours they appeared normal in every way. In none of these did the acetylcholine produce plastic rigidity. However, almost all of the animals showed some of the other signs described by FELDBERG and SHERWOOD. Thus immediately after the injection the animals appeared frightened, tended to hide themselves and, when touched, hissed and screamed. Then the cats started to scratch their heads, showed licking movements and in some cases salivation. Some of the cats after 5—10 minutes convulsed for a brief period.

These signs are in good agreement with those described by FELDBERG and SHERWOOD and suggest that the acetylcholine reached the same sites as in their experiments. The occurrence of plastic rigidity was, however, too infrequent for

a systematic study of its origin. The explanation is not yet found why so-called catatonia did not occur, except that, perhaps, this condition has not been defined with sufficient clarity.

Feldberg, W. and S. L. Sherwood, J. Physiol. 1954. *125*. 488.

Sten-Knudsen, O. (Institute of Neurophysiology, University of Copenhagen, Denmark): MECHANICAL RESPONSE AND MEMBRANE POTENTIAL DURING TRANSVERSE STIMULATION OF FROG MUSCLE.

Application of a transverse alternating current causes contraction in a whole muscle which has been rendered non-propagating by an excess of potassium in the Ringer's solution (KATZ and LOU 1947). Moreover, the amount of tension developed is graded with the strength of the applied transverse field (STEN-KNUDSEN 1954). This has been investigated in greater detail and the mechanical response has been compared with the change in membrane potential brought about by the alternating field.

The muscle (ext. long. dig. IV or isolated single fibres) was blocked by raising the potassium concentration in the Ringer's solution to 10—12 mM. Transverse stimulation was obtained by means of two platinum plates placed in parallel with the muscle. The membrane potential was measured with conventional microelectrodes and the A.C. pick up was eliminated by arranging the microelectrode in an A.C. bridge and adjusting to maximum rejection.

When isometric tension is plotted against strength of the alternating field S-shaped curves are obtained. The mechanical tension was reproducible within 10 per cent during increasing and decreasing fields. With a single fibre blocked with 10.5 mM K at 20° C tension rose at a field strength of 1 V/cm (1000 c/s) and at about 4 V/cm attained its maximum value which was 95—100 per cent of the maximum tetanus tension at the same length. With increasing potassium concentrations in the external medium maximum tension decreased to about half the full tetanus tension at 18 mM K. The optimum fre-

quency for the tension development was in the range of 600—1000 c/s (20° C) and the threshold of the field strength increased with increasing frequency, being 0.7 V/cm at 200 c/s and 3.5 V/cm at 5 kc/s.

With an A.C. field linearly increasing from zero to 6 V/cm the membrane potential depolarized to about —45 mV over a variation of field strength from 1 V/cm to 1.5 V/cm and remained at this level with the further increase in the field strength. The major part of the rise in the mechanical tension took place with the membrane potential at a (low) constant level.

Katz, B. and H. C. Lou, J. Physiol. 1947. *106*. 30 P.
Sten-Knudsen, O., J. Physiol. 1954. *125*. 396.

Stovner, J. (Institute of Pharmacology, University of Oslo, Norway): THE EFFECT OF TETRAETHYLAMMONIUM (TEA) ON MAMMALIAN MYONEURAL JUNCTION.

The autonomic ganglionic blockade produced by TEA is well known and has been fully elucidated. However, reports in the literature indicate that also on the mammalian myoneural junction TEA has a profound effect when the transmission has been depressed either by a specific neuromuscular blocking agent or by a deficiency of calcium. Under these circumstances TEA will partly restore transmission (KENSLER 1949, 1950). In the present work the action of TEA has been investigated on the normal mammalian myoneural junction, as well as on that depressed by a deficiency of calcium or an excess of magnesium. The isolated phrenic nerve diaphragm preparation from the rat has been used, as this can be adapted both for electrophysiological methods and for testing the sensitivity of the postsynaptic membrane to acetylcholine or potassium. In addition, experiments on rabbits and cats were performed.

On the normal rat diaphragm preparation concentrations of TEA up to 2 mM in the bath caused no depression of the

responses to either single or tetanic nerve stimulation. This concentration of TEA also caused no change in the action potentials of the phrenic nerve or the diaphragm muscle. The excitability and contractility of the muscle to direct stimulation were also unaltered by this concentration of TEA, as was the twitch produced by rapid injection of acetylcholine or potassium.

However, when the responses to nerve stimulation had been depressed either by lack of calcium or by excess of magnesium, a marked restoration could be effected with only 1 mM TEA in the bath fluid. On recording end-plate potentials in a medium with low calcium or excess magnesium, it was found that addition of TEA caused an increase in the amplitude of the end plate response without change in time course and without signs of repetitive responses.

In a calcium-deficient medium the twitch produced by injection of acetylcholine or potassium is greatly enhanced. When neuromuscular transmission was restored by TEA, the sensitivity to acetylcholine was lowered to normal, but the increased sensitivity to potassium remained.

On nerve-muscle preparations *in situ* in cats and rabbits, it was also found that TEA restored the responses evoked by nerve stimulation, when these were depressed by magnesium.

It is suggested that TEA causes an increased output of acetylcholine from the presynaptic nerve terminals.

Kensler, C. J., Fed. Proc. 1949. *8*. 307.
Kensler, C. J., Brit. J. Pharmacol. 1950. *5*. 204.

Thesleff, S. (Institute of Pharmacology, University of Lund, Sweden): A STUDY OF THE »DE-SENSITIZATION» PRODUCED BY ACETYLCHOLINE AT THE MOTOR END-PLATE.

Desensitization of end-plate receptors, due to prolonged action of depolarizing drugs, was studied with ionophoretic micro-application of acetylcholine (also of carbachol und suc-

cinylcholine). A steady dose producing an initial depolarization of 10 to 20 mV can cause nearly complete loss of sensitivity of local receptors within a few seconds. After withdrawal of the drug, local sensitivity recovers with an initial half-time of about 5 seconds. The hypothesis is put forward that receptor molecules can change from »effective« to »refractory« form.

Tribukait, B. (Aus der klinisch-physiologischen Abteilung, Karolinska Sjukhuset, Stockholm, Schweden): EINE METHODE ZUR BESTIMMUNG DER TOTALHÄMOGLOBINMENGE VON LABORATORIUMSTIEREN MIT EINIGEN BEISPIELEN IHRER ANWENDUNG.

Die von GEMZELL und SJÖSTRAND (1954) angegebene Methode zur Bestimmung der Totalhämoglobinmenge von Kleintieren mit CO ist, um grössere Genauigkeit zu erreichen, weiterentwickelt worden.

Innerhalb eines geschlossenen Systems befindet sich in einer Glaskammer das Versuchstier (Ratte, Meerschweinchen, Kaninchen). Eine Pumpe sorgt für ständige Cirkulation der Luft, die dabei durch einen KOH-Filter von CO_2 befreit wird, gleichzeitig wird durch ein Ventil der veratmete Sauerstoff ergänzt. Das Gesamtvolumen und die O_2-Concentration des Systems bleiben so während beliebiger Zeit konstant. Nachdem eine bekannte Menge CO dem System zugeführt worden ist, verweilt das Tier so lange darin, bis sich ein Gleichgewicht zwischen der CO-Concentration des Systems und der COHb-Concentration eingestellt hat. Aus der CO-Concentration, bestimmt nach der Methode von LINDERHOLM und SJÖSTRAND (1956), und dem Volumen des Systems wird die vom Tier aufgenommene CO-Menge berechnet. Diese ist direkt abhängig von der Totalhämoglobinmenge und der O_2-Concentration. Der mittlere Fehler für die gemessene Total-Hb-Menge beträgt ± 2 %. Die Bestimmung kann am selben Tier beliebig oft und ohne Schaden wiederholt werden.

Folgende Beispiele der Anwendung der Methode werden demonstriert:

1. Regeneration der Total-Hb-Menge nach akuten Blutungen bei normaler und eisenreicher Nahrung.

2. Verhalten der Total-Hb-Menge unter Hyper- und Hypoxie verschiedener Stärke.

3. Die Wirkung sogenannter Hämatopoietine auf die Total-Hb-Menge.

Gemzell, C. A. und T. Sjöstrand, Acta Physiol. Scand. 1954. *30*. 369.
Linderholm, H. und T. Sjöstrand, Acta Physiol. Scand. 1953. *37*. 240.

Valen, E. (Institute of Zoophysiology, University of Oslo, Norway): ASPHYXIA IN INSECTS.

When an insect or a spider is enclosed in an airtight chamber, it will eventually replace all the available oxygen by carbon dioxide. In an atmosphere of pure oxygen the CO_2 concentration may rise to some 97 % or more without being lethal to the animal. The oxygen consumption during the entire asphyxia is somewhat higher than the normal resting metabolism and there is no apparent retardation of the rate of oxygen consumption in spite of the enormous accumulation of CO_2. These phenomena will be discussed in relation to other respiratory peculiarities described in insects.

Whittaker, V. P. (ARC Institute of Animal Physiology, Babraham, Cambridge, England): THE RENAL EXCRETION OF PHLORIZIN IN THE DOG.

An account will be given of work done on this subject with Drs W. Braun and W. D. Lotspeich at the University of Cincinnati College of Medicine.

Phlorizin was estimated in urine and ultra-filtrates of plasma by the Folin-Ciocalteu method for phenols after sep-

arating interfering substances by paper chromatography. Preliminary experiments showed that phlorizin was in part rapidly converted to the glucuronide and that both phlorizin and its glucuronide are bound to plasma protein to the extent of 25—55 %. At a plasma phlorizin concentration of 1 mg/100 ml the simultaneous phlorizin/creatinine clearance ratio was about 4, suggesting active tubular secretion of phlorizin. With increasing plasma concentration, phlorizin secretion was self-depressing, the clearance ratio falling to unity at 5 mg/100 ml. Phlorizin secretion was also abolished by Benemid and *p*-aminohippuric acid (PAH).

The excretion of phlorizin glucuronide was also followed, but only in the presence of phlorizin, owing to the non-availability of the pure glucuronide. The simultaneous phlorizin glucuronide/creatinine clearance ratio was unity at plasma phlorizin glucuronide levels of 1—5 mg/100 ml (expressed as phlorizin). However, when Benemid or PAH was administered the clearance ratio rose perceptibly, assuming values between 1.5 and 2.0. A possible explanation of these results is that phlorizin glucuronide is excreted by a phlorizin sensitive, Benemid and PAH insensitive pathway which in the presence of phlorizin is freed for glucuronide transport only when the transport of phlorizin itself is inhibited by other means. Alternatively, phlorizin glucuronide may normally be synthesized in the liver and excreted by filtration alone, but when phlorizin transport is suppressed by Benemid or PAH, additional amounts of phlorizin glucuronide may be synthesized by the kidney and added to the filtered load. Experiments to distinguish between these alternatives are being devised.

The relation between phlorizin glucuronide formation and glycosuria was studied in experiments in which the time course of glucose, phlorizin and phlorizin glucuronide excretion was followed after a short infusion of phlorizin. Free phlorizin rapidly disappeared from the urine, but glucose and phlorizin glucuronide excretion persisted, declining *pari passu* over a number of hours. The significance of all these results for our understanding of the mechanism of phlorizin glycosuria will be discussed.

*Wollheim, F. (Institute of Pharmacology, University of Lund, Sweden): ON THE ELIMINATION OF BROMINE-CONTAINING HYPNOTICS.

This investigation deals with 3 bromine-monoureids namely bromodietylacetylurea (= carbromal), N-acetyl-N-bromodietylacetylurea (= acetylcarbromal) and α-bromisovalerylurea (= bromisoval) and one barbituric acid, allyl-β-bromallyl-barbituric acid (= vesperon, trademark).

We wanted to learn how these substances were changed in the human body, with a certain respect to the organic bromine. There are some papers dealing with chronical bromoureid-intoxication indicating the possible role of ionised bromine in these instances. Earlier reports on bromine excretion after intake of therapeutic bromoureid doses are very rare, mostly about 40 years old, and have left somewhat conflicting results, I suppose partly because of methodological errors. Some recent investigations with reliable methods refer only to newly synthezised substances.

The bromine determination was undertaken with a method based on the van der Meulen reaction

$$Br^- + 3\ ClO^- = BrO_3^- + 3\ Cl^-.$$

It has been much used during the last 20 years for work with biological material. It is accurate even when small amounts are to be determined and the chloride always present does not interfere.

The correct separation of organic and ionic bromine was performed by precipitating the latter with silvernitrate and immediate removal of the silver excess. This proved to be necessary for preventing the splitting of the rather labile organic bromine linkage.

The material consists of 25 patients at the University Clinic of Lund, whose urine was collected for 2—4 weeks. They were given varying doses of the substances. After feeding the monoureids the urine contained for a few days some

* Paper read at the pharmacological meeting August 30th.

organic bromine. This amounted to 1—2 % of given bromisovalbromine, 5—10 % of carbromal and acetcarbromalbromine. The remaining bromine came out ionised in the typical slow manner. Of the vesperonbromine about 35 % was excreted in organic linkage and consequently the total bromine came out much faster.

Wretlind, A. (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden): PHARMACOLOGICAL PROPERTIES OF NEUTRAL FATS.

In attempts to produce fat emulsions for intravenous nutrition experiments with low-molecular neutral fats were performed. In tests with an emulsion of tributyrin, injected intravenously, symptoms appeared that had not been observed after far larger doses of, *e. g.*, olive oil or cottonseed oil emulsions. The animals lost their righting reflexes, and a relatively lengthy apnoea appeared, followed by violent hyperpnoea. In addition, salivation, miosis and bradycardia were present.

The effect of tributyrin on circulation is characterized by rapidly appearing bradycardia and a fall in blood pressure, followed by a rise in blood pressure. Bradycardia and the fall in blood pressure are inhibited by vagotomy and procaine. They do not appear with injection into the left ventricle, aorta or large arteries. The effect is probably elicited through receptors with afferent pathways in the vagus, and located at the right side of the heart or the lungs. — The rise in blood pressure is largely due to contraction of peripheral blood vessels. This rise is not inhibited by tetraethylammonium, hexamethonium, dihydroergotamine, ergotamine or procaine. In the heart-lung preparation, tributyrin decreases the heart action. The blood flow in the abdominal aorta is reduced, together with a rise in blood pressure, after injection of tributyrin.

The apnoea produced by tributyrin is not elicited after vagotomy, but appears after administration of atropine or procaine. Injection into the left ventricle, aorta or large arteries does not produce apnoea. Apnoea is probably evoked via receptors in the right side of the heart or the lungs. — The

hyperpnoea, which follows the apnoea, is considered to b partly produced by central stimulation.

Emulsions containing triisovalerin or tricapronin produce the same pharmacological effects as tributyrin.

LD_{50} of tributyrin on intravenous injection into mice wa found to be 320 ± 11 mg/kg. On the basis of this surprisingly high toxicity of tributyrin the toxicity of other low-molecular triglycerides was investigated. The LD_{50} was found to be lowes in triisovalerin (82 ± 4 mg/kg) and to increase when the fatty acid chain contains less than 5 carbon atoms, reaching 1.600 ± 81 mg/kg in triacetin. With more than 5 carbon atoms in the fatty acid chain, LD_{50} rises successively and lies over 10.000 mg/kg for trinonylin, tricaprinin and triundecylin.

Stockholm 1957, Klara Civiltryckeri AB